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THE PREVALENCE OF YAWS (FRAMBESIA TROPICA) IN THE UNITED STATES*

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Among the more serious diseases of the tropics, yaws or frambesia tropica is of interest not only because it is striking in appearance, easily communicable and disabling, but also because of its close resemblance in many respects to syphilis. Though often simulating syphilis both clinically and pathologically, it is a much less serious disease, as it does not attack the central nervous system or viscera and is not transmitted by heredity. It is, furthermore, much more easily eradicated by arsphenamin than is syphilis. It is with the object of discussing the prevalence of yaws in the United States and recording a case recently observed in New York that this communication has been written.

REPORT OF CASE

History.—L. C., aged 18 years, unmarried, a full blooded negress, born in Montserrat, British West Indies, applied for treatment at the dermatologic department of the Harlem Hospital, Nov. 30, 1921. Her parents and an only brother, aged 17 years, were living and well. None of her family, to her knowledge, had ever suffered from a similar disease. She did not remember having had any of the diseases of childhood and had been attended only once in her life by a physician, when suffering from cramps incident to menstruation. The menses were established at 13, and since then had been regular.

The patient had lived all her life on the island of Montserrat until July 10, 1921, when she sailed for the United States, arriving in New York, July 22. About two weeks before leaving Montserrat, she had come in contact with two young children who were suffering from sores on the face and hands. On inquiring of the parents as to the nature of these sores, she was told that a physician had said that the children were suffering from yaws. On arriving in New York, she secured work by the day as a housemaid. As far as she was aware, none of the people with whom she came in contact had any disease

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Fig. 1.—Generalized eruption consisting of individual and grouped lesions covered with crusts, some of them suggesting the appearance of a corymbiform syphilid.

of the skin. The patient was certain that she had been entirely free from any eruption until November 10, when she noticed on her right thigh a "pimple" which occasioned considerable itching. It grew larger and in a few days attained its maximum size, that of a 5-cent piece.

Coincident with the first appearance of this lesion, she began to suffer from headache and rheumatic pains in the left shoulder and chest and from sore throat. The pains had continued to the time of treatment. She had not suffered from malaise or fever. About one week after she had first noticed the lesion on the thigh, the rest of the eruption which she now presented made its appearance. Some of these lesions, she stated, lasted only a few days, leaving a scaly surface after their disappearance. She said that she had had sexual intercourse only once in her life, five or six weeks before the appearance of the eruption.

Physical Examination.—Examination revealed that the patient was well nourished and in apparent good health. She weighed 125 pounds (57 kg.) and was 5 feet and 1 inch (1.5 meters) in height. The eruption consisted of about thirty individual and grouped lesions, varying in size from that of a split pea to that of a silver quarter. They were distributed as follows: on the scalp, there were six lesions; on the face and neck seven (the largest being about the size of a 10-cent piece), and on the trunk and arms, twelve, the largest being the size of a quarter. In the midscapular region were two large lesions surrounded by a number of smaller satellites resembling a corymbiform syphilid. The eruption on the lower extremities was confined to a single lesion on the anterior aspect of each thigh and a flattened macerated patch on the sole of the right foot, the macerated appearance being partly due, perhaps, to a poultice which she had applied.

The individual lesions were all painless, and fairly firm to the touch. They gave the appearance of being superficially attached to the skin. Some of them were dry and scaly; others were covered with dirty, yellowish crusts, suggesting an impetigo. All of the lesions, except the dry ones in process of involution, exuded pus on pressure; and, when the crusts were removed, a red, papillomatous, raspberry-like surface was presented. When the lesions were irritated by friction, there was a profuse serous discharge. Under the breast, there was a patch from which the crust had been removed by friction and maceration, giving the appearance of a syphilitic condyloma. The mucous membranes of the mouth and genitalia were entirely free of any eruption. The palms were also unaffected. The eruption did not cause any disagreeable odor, the patient being very cleanly in her habits.

Laboratory Examinations.—Examination by dark-field illumination of the serous discharge revealed large numbers of spirochetes indistinguishable (by the ordinary observer) from *Spirochaeta pallida.* These examinations were made on several occasions by Dr. Howard T. Phillips (a former associate). A Wassermann test by the New York Board of Health was reported negative, December 2, while a similar examination by Dr. Oliver Hillman gave a four plus reaction with both cholesterinized and crude alcoholic antigens.

Animal inoculations were made by Drs. Wade H. Brown and Louise Pearce of the Rockefeller Institute, who reported: "Examination of fluid obtained from several nodules from patient L. C., Dec. 20, 1921, showed an abundance of long and delicate spirochetes of the type *Treponema pertenue.* Inoculations were made from this fluid into the testicles of four normal rabbits. One of the animals inoculated developed a secondary bacterial infection. The others

showed practically no immediate reaction. Within three to four weeks, there was a definite inguinal adenitis in all animals, and there was suggestive enlargement and increased tension of the testicles. The adenitis persisted for some time. The testicular condition, however, subsided. At the end of six weeks, transfers were made from lymph nodes of two of the original animals. These animals gave a reaction analogous to those of the first group, but the lesions which developed in the testicles were very slight, consisting chiefly in slight swellings and increased resistance, with some thickening of the tunics.

"Castration of one of these animals performed eleven weeks after inoculation showed slight but definite enlargement of the testicle, diffuse thickening of the tunics and a small nodule situated in the region of the head of the epididymis. There was also well marked adenitis in this animal. Dark-field examination of material showed no spirochetes, but this material was used for a third series of transfers.

"Examination of another animal inoculated with material from lesion of patient showed, at the end of seventeen weeks, a condition which was more characteristic. Both testicles were slightly enlarged, somewhat congested and over the surface of the tunics there were a number of minute granulomatous nodules which were identical in all respects with tunic nodules, which we have frequently observed in the strain of yaws, originally isolated by Dr. Nichols and studied in this laboratory during the last year.

"The mild reaction in the testicles which followed inoculation of comparatively large numbers of actively motile spirochetes associated with slight but definite lymphadenitis, and finally the production of the tunic lesions described, leads us to believe that there is very little doubt that the infection in this case is due to *Treponema pertenue* rather than to *pallidum*."

Histologic Examination.—December 8, a piece of tissue was excised from the chest, under local anesthesia, and the following histologic report was made by Dr. Walter J. Highman:

"Low Power Zeiss, Ocular 4, Objective A. Epidermis is found thrown up in almost verrucous manner and on account of confluence of strands of epidermis inclusions of papillae are established which resemble small islands. Within these, as well as in the corium underlying the epidermis, is an infiltration.

"High Power, Ocular 4, Objective D.D. The infiltration in the islands is found to consist of lymphoid and epithelioid cells in a lacey network of connective tissue fibers, a high degree of edema present and occasional actual minute abscesses. In the corium the infiltration in general has the same character but added thereto are numerous foci consisting almost entirely of plasma cells filling perivascular spaces about the arterioles, which themselves have slightly, if at all, thickened walls and swollen endothelium.

"Comment: The conditions simulated are tuberculosis verrucosa, syphilis, blastomycosis, sporotrichosis and kerion. Tuberculosis verrucosa is excluded by lack of giant cells and the large number of plasma cells. Syphilis can be less readily excluded but gummas practically never show the verrucoid appearance here exhibited and the vascular changes are on the whole not sufficiently profound. The other three conditions are excluded by the relatively small number of true abscesses. By exclusion, diagnosis remains: Yaws."

Diagnosis.—The patient was presented before the Dermatological Section of the New York Academy of Medicine, December 6 by me (in conjunction with

Dr. B. F. Ochs) as a questionable case of frambesiform syphilis.[1] Having had no previous experience with yaws and having had little opportunity to study the case, we did not wish to hazard a diagnosis of this disease. Dr. Herman Goodman, the only one present who had had any personal experience with yaws, made a diagnosis of this disease from the clinical appearance. Dr. Pearce, who had recently seen cases of yaws in Africa, saw the patient a few days later, and unhesitatingly agreed with this diagnosis, on clinical grounds.

Treatment.—The treatment consisted solely of six intravenous injections of neo-arsphenamin, administered during a period of seven weeks, beginning, Dec. 22, 1921. After the fourth injection, the eruption had entirely disappeared, leaving a brownish pigmentation, which had persisted to the time of writing. The dosage of the first two injections was 0.45 gm., and of the succeeding four injections, 0.6 gm. The subjective symptoms, including headache and pain, had entirely disappeared one week after the first treatment. A second Wassermann test made, April 21, 1922, by Dr. Hillman was reported as plus minus.

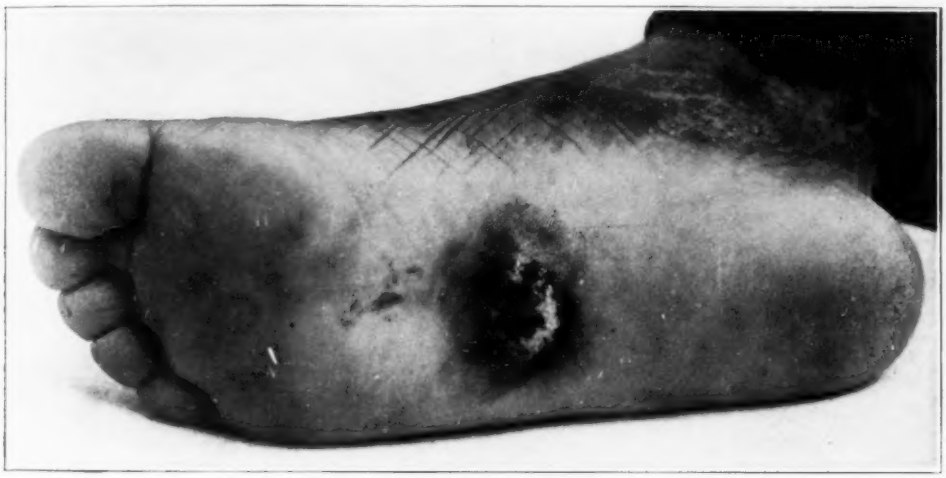

Fig. 2.—Large individual macerated yaw of the sole.

Summary.—The patient, a negress of 18, who came directly to New York from the West Indies (Montserrat) where she had always lived and where she claimed to have been exposed to yaws two weeks before sailing, after nearly four months residence in New York developed a generalized eruption which corresponded with descriptions of yaws and which was so diagnosed by two observers who were familiar with the disease. There was a general adenopathy. There were no lesions of the mucous membranes. Spirochetes were found by dark-field illumination. The Wassermann test was positive, and the eruption cleared up readily under neo-arsphenamin. The histologic diagnosis by exclusion was yaws, and the result of rabbit inoculations strongly favored the same diagnosis. The conclusion would, therefore, seem warranted that the patient was suffering from yaws, and that the infection had been imported from the West Indies (where the disease is common) to New York, where even a single case appears to be a great rarity.

1. Fox, Howard: Arch. Dermat. & Syph. **5**:411 (March) 1922.

THE LITERATURE

The question of the occurrence of yaws in the United States was discussed in 1915 by Edward J. Wood.[2] He attempted briefly to mention every case that had been reported in the United States previous to his publication as he had found "the records of yaws in the literature so few." In addition to recording a case of his own, he was able to find only eight other case reports, one of which concerned a patient observed in Canada. I have also been surprised at the small number of cases recorded in this country and have only been able to find a few additional cases which had not been included by Wood and a few cases subsequently reported.

According to Wood, the first authentic reference to yaws in American literature is to be found in a volume by Brickell on the Natural History of North Carolina, etc., published in 1737. In the course of his description, this early writer says "The Yaws are a disorder not well known in Europe but very common and familiar here. It is like the Lues Venerea having most of the symptoms that attend the Pox, such as Nocturnal pains, Botches, foul Eruptions and Ulcers in several parts of the body....This distemper was brought hither by the Negroes from Guinea where it is a common distemper among them. This distemper though of a venereal kind, is seldom cured by Mercurials, as I have often experienced." According to Joseph Jones,[3] the first recorded observations on yaws as occurring among the negroes of Louisiana were made by Du Pratz in 1758, in his "History of Louisiana." The author mentions yaws in giving advice to prospective purchasers of negro slaves, saying in the course of his remarks, "You must ask your examining surgeon if he is acquainted with the distemper of the yaws which is the virus of Guinea and incurable by a great many French surgeons though very skillful in the management of European distempers." Roman, is his history of Florida, in 1776 (quoted by Jones) writes " I have seen three or for instances of the disease called body yaws (in the islands) and in Carolina the same distemper. Mercurial medicines are used against it."

Humphreys,[4] in a letter written to Benjamin Rush in 1770, said that among a number of slaves "was a lad about 18 years of age who was a miserable object; from the disorder called the yaws; he was vastly more affected with it than any person I ever saw, before or since; from his head to his feet he was thickly set with those sorts

2. Wood, E. J.: The Occurrence of Yaws in the United States, Am. J. Trop. Dis. **2**:431 (Jan.) 1915.

3. Jones, J.: Medical and Surgical Memoirs of Various Diseases, New Orleans **11**:1184, 1887.

4. Humphreys, T.: Minutes of a Case of Yaws, Philadelphia Med. Museum **1**:442, 1805.

of knots or ulcers which that disorder produces when it is in its worst stages."

Van Zandt,[5] in 1831, reported a case of yaws seen in New York. The patient was a negro cook on board a vessel from the West Indies, who stated that previous to sailing he had slept in a bed in which a "negro had died with the yaws." The disease appeared after he arrived in New York. There were febrile symptoms for a few days, followed

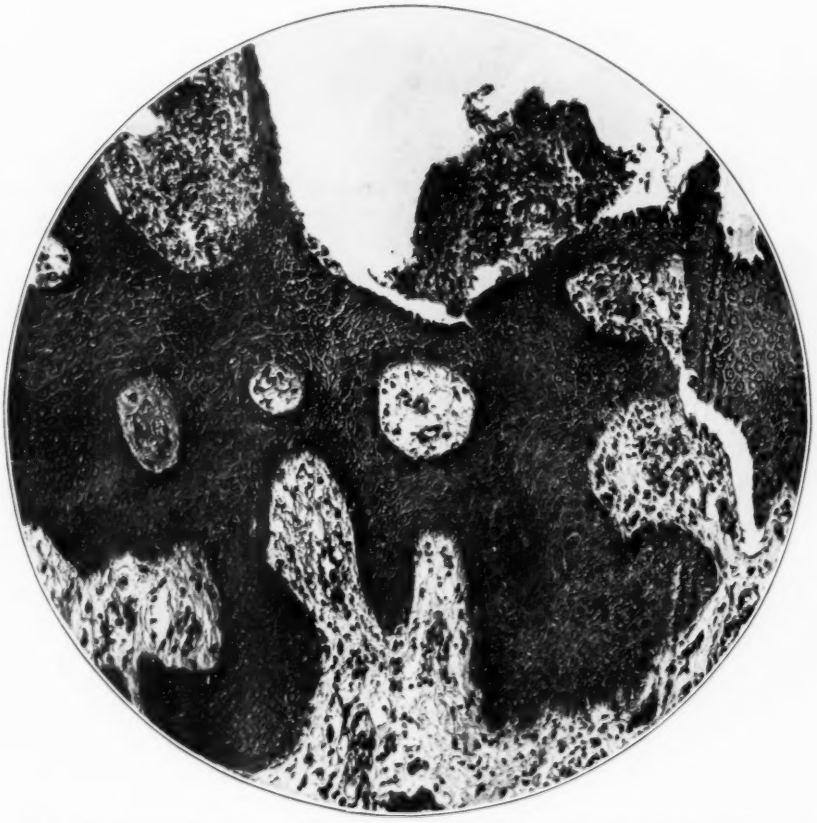

Fig. 3.—General topography of frambesia lesion showing high degree of epidermal hyperplasia (acanthosis) with island-like inclusions of papillae. At the upper left hand corner is an abscess and there is a similar one at the upper right below crust. The distribution of the infiltration is clearly shown. (Low power.)

by an eruption of small pimples not larger than a grain of mustard seed which later became protuberant pustules. One crop of pustules followed another in regular succession. When the patient was nearly convales-

5. Van Zandt, C. A.: Case of Yaws, New York Med. Chirurg. Bull. **2**:4 (Nov.) 1831.

cent, there were painful hard swellings of the soles. It is interesting, in view of the present almost miraculous remedy (arsphenamin) for yaws, to read the formulas of seven different prescriptions which the writer had used in treating this patient.

McDowell,[6] in 1858, wrote a short and rather unsatisfactory report entitled "Framboesia or Yaws." The patient was a negro infant of 2 years. He presented an ulcerating, fungoid growth about the anus which was large enough to interfere with defecation. His mother was a native of Africa and was said to have had the "same disease." About three months previously, the child had had fever and "an eruption over most of the body."

Cartwright,[7] in the following year, reported a case of yaws associated with vesicorectovaginal fistula. The patient was a negress in New Orleans. The eruption involved the nates and lower abdomen as far as the umbilicus. "Hard excrescences had formed on the spots occupying the integuments of the labia and through fissures in these excrescences granulated pallulations resembling mulberries had protruded distilling a very fetid ichorous humor. The mama pian or mother yaw was situated near the upper commissure of the right labium majus." There were torturing pains by night, and inguinal swellings which were painful and hard but not suppurating.

Doane,[8] in 1876, wrote a brief and unconvincing report entitled "A case of yaws framboesia or fungoid growth arising from syphilis." The patient was a negress of 35, from Jamaica. The writer stated that she "had a growth (resembling raspberries placed in layers) upon the external and outward portions of the right leg. There was also a small ulcer, undoubtedly syphilitic in its origin. On pressing over the tibia, great pain was caused and upon the back syphilitic papules were seen causing some itching." The writer added that the patient had been seen in consultation with Dr. E. L. Keyes, Sr., "who pronounced the above diagnosis of yaws correct."

Jones,[9] in 1878, reported a case of yaws in New Orleans in a thorough and painstaking manner. His patient was a sailor, born on an island on the coast of Africa. His father was a native of France, his mother of Africa. He stated that he had contracted the disease three months previously, his ship having been visited by natives suffer-

6. McDowell, G.: Framboesia or Yaws, New Orleans M. J. **15**:192 (March) 1858.

7. Cartwright, S. A.: Case of Framboesia and Vesico-Recto Vaginal Fistula, New Orleans M. J. **15**:512 (July) 1859.

8. Doane, L. G.: A Case of Yaws Framboesia or Fungoid Growth Arising from Syphilis, Pharmacist & Physician **9**:6 (Aug.) 1876.

9. Jones, J.: Observations on the African Yaws, etc., in Insular and Continental America, New Orleans M. & S. J. **5**:673 (March) 1878.

ing from yaws. During the voyage, he had suffered from severe constitutional symptoms. The eruption first appeared on the face as vesicles, drying to form crusts. It became generalized and was especially severe on the fingers and toes, with swelling and ulceration of the phalanges.

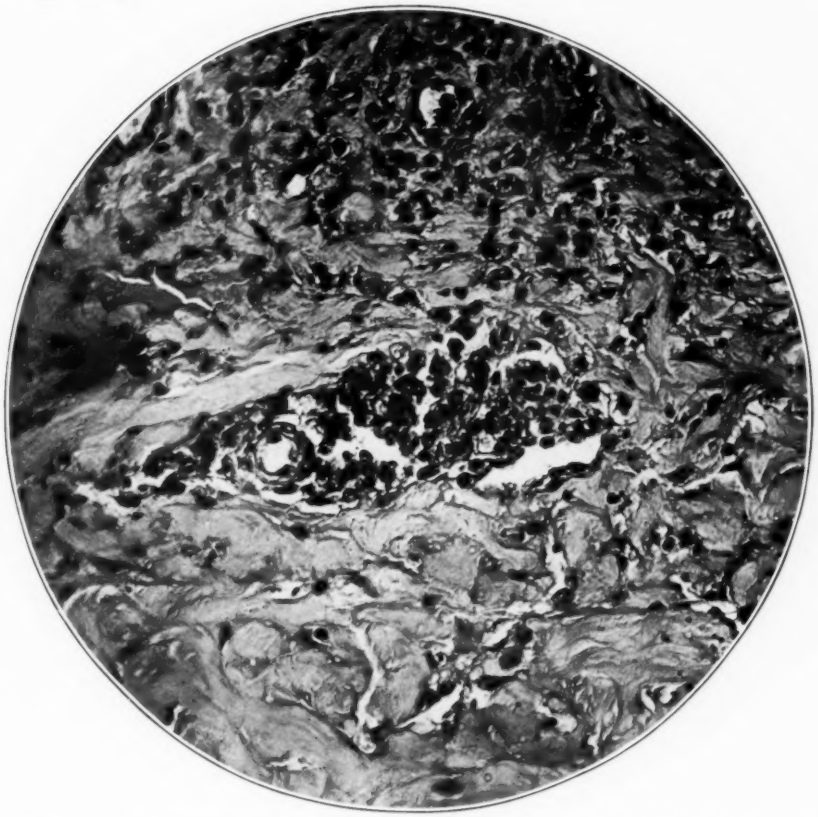

Fig. 4.—Two features of the frambesia lesion stand out in this section: In the center is a transsected arteriole, the perivascular space of which is distended by an infiltration, prevailingly of plasma cells. The vessel itself is but slightly altered, if at all. The independent infiltration above is in vague relation to venules and consists of lymphocytes, a few plasma and epithelioid cells, and a moderate number of fibroblasts. This area, with more vascular changes, would be suggestive of syphilis. (High power.)

McCosh,[10] in 1895, presented a case before the New York Surgical Society as "syphilis cutanea vegetans or framboesia." The report was brief, not mentioning yaws and merely describing a "papillomatous excrescence on the tip of the nose which looks much like a large rasp-

10. McCosh, A. J.: Syphilis Cutanea Vegetans or Framboesia, Ann. Surg. **21**:46 (Jan.) 1895.

berry." Microscopic examination revealed simple inflammatory tissue. The patient who was an unmarried woman, about 24 years old, had previously suffered, at different times, from rhinitis and sores on the roof of the mouth, throat and nasal septum.

Matas,[11] in 1896, writing in Dennis' "System of Surgery," spoke of two patients with yaws in New Orleans. One, he said, was an imported case, that of a mulatto from Mauritius, seen in 1877; the other patient was a full blooded negro seen in 1895. "This patient," he wrote, "was a Louisianan by birth and there is no clue in his history by which contagion may be traced. Still we are loath to believe that this disease can originate de novo in the United States." A photograph showing the patient's face, with numerous warty excrescences that were also said to cover the body, certainly seemed to present a condition characteristic of yaws.

McMurran,[12] in 1900, in a communication entitled "Yaws and Smallpox," described the clinical symptoms of the two diseases and followed with a report of a classic case of smallpox, for comparison with the report of a somewhat different condition which he surmised might be yaws. An epitome of this report, which was not very convincing, was as follows: The patient was an unmarried woman of 24, who, on the preceding night, had complained of pains in her back. There was no inflammation of the mucous membranes of the mouth and throat. The temperature was 101 F., pulse 100, respirations 20. The next morning the temperature was 100 F. On the fifth day, there was a vesicular eruption on the forehead and hands and a slight eruption on the breast. At this time, the temperature, pulse and respirations were normal. Her condition continued to improve, with no impairment of health. "The tubercles peeled off and I did not observe any pitting on her face." The patient had never been vaccinated.

In 1910, Nichols and Siler,[13] in separate communications, reported a case of yaws, from both the clinical and pathologic standpoint. The patient was a colored soldier returned from the Philippines, where, according to the writers, his infection had probably occurred. This entailed the rather long incubation period of eighty-six days. The clinical diagnosis was made when the patient was suffering from his second crop of lesions, appearing as typical fungoid papules covered with dirty, yellowish crusts. *Spirochaeta pertenuis* was found by dark-

11. Matas, Rudolph, in Dennis' System of Surgery, New York and Philadelphia, Lea Brothers & Company **4**:866, 1896.

12. McMurran, R. L.: Yaws and Smallpox, Virginia M. Semi-Month. **4**:646 (Feb. 9) 1900.

13. Nichols, H. J.: Yaws: with a Demonstration of Infected Tissue, Proc. New York Path. Soc. **10**:1 (Feb. and March) 1910. Siler, J. F.: Report of a Case of Yaws, Mil. Surgeon **27**:306 (Sept.) 1910.

field illumination in the serous exudate. The Wassermann reaction (Noguchi method) was negative. Inoculation of a monkey's eyebrow was positive, the spirochaeta being found and transferred to rabbits testicles, and transmitted through five generations.

White and Tyzzer,[14] in the following year, recorded another imported case of yaws in the person of a Porto Rican sailor. While the eruption was not at all typical of yaws, a probable clinical diagnosis of this disease was made by exclusion. The eruption consisted of "four strange looking, elevated, dry, tumor masses unaccompanied by any signs of local or general inflammation or disturbance." There was also a general and marked glandular enlargement. The Wassermann reaction was negative (Noguchi method). Puncture of a gland showed "a small infrequent spirochaeta which corresponded sufficiently with Castellani's *Spirochaeta pertenuis.*" Inoculation of the eyebrow of a monkey was successful, lesions appearing at sites of inoculation after a period of incubation of sixteen days. Inoculation of the cornea of ten rabbits was unsuccessful. A detailed histologic examination revealed that the epidermis was "markedly acanthotic and hyperkeratotic or moderately parakeratotic." The cutis showed a marked mononuclear infiltration with no giant, epithelioid or plasma cells, the vessels being normal except for moderate dilitation.

Lyle,[15] in 1912, reported a case of "gumma of the liver as a sequel to yaws." The patient was a man, 46 years old, from the West Indies, who gave a history of having yaws thirty-nine years previously. As confirmatory evidence, he stated that at that time he had been isolated, together with two other members of his family, in a "hospital given over to the treatment of yaws." There was no history of syphilis, and a positive Wassermann reaction was obtained only after a provocative injection of arsphenamin. The case was recorded as disproving the relationship between syphilis and yaws as "it has been claimed that an attack of yaws gave an immunity to syphilis."

Wood, in 1915, reported what he considered to be a case of yaws in North Carolina, in an infant whose "parents had always lived in that state and at no time had come in contact with any one from the West Indies or other endemic center of the disease." The importance that this case would assume is unfortunately greatly lessened from the fact that the diagnosis was only made later in retrospect from a study of notes and photographs. There is no mention of any search for spirochetes or of a Wassermann test having been made. The patient was an infant of 5 months who presented a generalized, fungating

14. White, C. J., and Tyzzer, E. E.: A Case of Framboesia, J. Cutan. Dis. **29**:138 (March) 1911.

15. Lyle, H. M. H.: Gumma of the Liver as a Sequel to Yaws, Ann. Surg. **55**:111 (Jan.) 1912.

pustular eruption, part of which was shown by accompanying photographs. The lesions appeared in crops, were autoinoculable and were accompanied by itching and constitutional symptoms. The palms and soles were affected and there was a dactylitis. There was no glandular enlargement. When the patient was seen four years later, there was only a scar on the forehead to indicate the past trouble. According to the mother, all the children in the house had had the disease in milder form.

Davis,[16] in 1916, briefly reported two cases of yaws in a girl of 6 and a brother of 11 years who had apparently acquired the disease during a visit to Porto Rico. The eruption appeared after their return to this country. "The little girl showed one lesion on the lower lip, two in the right popliteal space and one typical cauliflower growth about 3 inches above the right popliteal space and one a few inches below. The boy had a few lesions of the same character on the legs. There was one sister at home who had a very large lesion on the buttock."

Evans,[17] in the following year, reported, in a brief and casual manner, two cases in which the patients were supposedly suffering from some manifestation of yaws contracted in tropical countries. The first patient was a returned missionary, from the South Sea Islands. He gave a history of suffering from frambesia eleven years previously. He presented "callouses or nodules about the size of a grain of wheat on the palmar surface of the index finger and thumb of the left hand. These were itchy and painful. There was also a small elevated spot in the left nostril." The lesions had been present two weeks or less. The second patient was a man who had served in the Philippines during the Spanish-American War. Since then, he had suffered from painful, recurring crops of vesicles and pustules of the soles, causing great pain and difficulty in walking. No spirochetes were found by staining. The eruption disappeared and did not return after one injection of 0.6 gm. arsphenamin.

Stephenson,[18] in 1920, reported fully the case of an American sailor in whom yaws developed while he was stationed at Brest, France. The writer thought the infection probably took place in a barber shop which was patronized by French Colonial troops recently returned from Africa. The patient was transferred to the United States, with the diagnosis of impetigo contagiosa. The eruption consisted of "crusted, circumscribed and pustular foul smelling lesions" of face, scalp and

16. Davis, C. N.: Yaws (Familial), J. Cutan. Dis. **34**:466 (June) 1916.

17. Evans, E.: Yaws: A Clinical Report of Two Cases, Wisconsin M. J. **15**:380 (March) 1917.

18. Stephenson, C. S.: Yaws; with Report of a Case which Developed in a Temperate Climate, Mil. Surgeon **47**:344 (Sept.) 1920.

penoscrotal junction. Some were "granulomatous and not unlike a fig in both color and consistence." When the eruption appeared, the patient had been away from Brest more than nine months. On admission to hospital, the diagnosis of frambesiform syphilis was made. The Wassermann reaction was positive. He was taken to the Vanderbilt Clinic, where opinions differed, the majority considering the disease to be syphilis. However, a Brazilian dermatologist was present that day, and he made the unhesitating diagnosis of yaws. Examination of serum from lesions showed spirochetes. Under arsphenamin, the eruption promptly cleared up and in ninety days the patient was returned to duty. The Wassermann reaction was then negative. A histologic examination revealed acanthosis and a plasmoma and marked polymorphonuclear infiltration, with here and there small abscess formation. There was an absence of changes in the vessels and connective tissue, suggestive of syphilis.

Schamberg and Klauder,[19] in 1921, published an elaborate study of a case of yaws in the person of a white American soldier returned from service in France. The eruption involved the palms, soles, scalp, forearms and penis. There were "brownish-yellow crusts which on being detached disclosed a raw surface consisting of red or yellowish fungoid granulations, secreting a thin, slightly purulent secretion." He gave no history of syphilis. Dark-field examination of the skin lesions showed "spirochetes with the morphological characteristics of *Spirochaeta pallida*." The Wassermann reaction was four plus with several types of antigen. There was a successful inoculation of rabbit testicles, but failure to produce corneal and scrotal lesions in the rabbit by intravenous injection of blood in the acute stage. Several attempts were also made to inoculate a monkey, but without success. The eruption entirely disappeared after a second full dose of neo-arsphenamin. A histologic examination, revealed hyperkeratosis and acanthosis of the epidermal tissue and extensive lymphoid and polymorphonuclear infiltration of the corium, with absence of blood vessel changes. Spirochetes were found in the "leukocytic areas of the apices of the papillae subadjacent to the rete."

FURTHER REFERENCES TO CASES

In the search for further references to cases of yaws in the United Stated, some dermatologic statistics were consulted. In 1914, a report of the committee on statistics of the American Dermatological Association was published by the chairman, Dr. S. Pollitzer.[20] This was

19. Schamberg, J. F., and Klauder, J. V.: Study of a Case of Yaws Contracted by an American Soldier in France, Am. J. Trop. Med. **1**:49 (Jan.) 1921.

20. Pollitzer, S.: Report of the Committee on Statistics of the American Dermatological Association, J. Cutan. Dis. **32**:312 (April) 1914.

a combined report from various clinics scattered over the United States. It covered a period of thirty-four years, from 1877 to 1911 inclusive, and contained a tabulated list of more than 679,376 cases. In this enormous total, there were only twenty-eight cases of yaws. Thinking that even this very small number of cases had been largely observed in some of the southern clinics, I consulted the individual annual reports of previous years and was surprised to learn that none of these cases had been reported from the south. Of the twenty-eight cases, twenty were reported from Boston alone, twelve of these being seen in the year 1878. Of the remainder, three were reported from Chicago, one each from New York and Philadelphia and two from cities not mentioned. The fact that the great majority of these patients were observed in the large seaports strongly suggests that the disease was imported from some foreign country. In the statistical report of the American Dermatological Association from the year 1916, a total of more than 58,000 cases were reported from seventeen different cities, and not a single case of yaws was mentioned.

OPINIONS AS TO PREVALENCE OF THE DISEASE

It is evident from the small number of cases of yaws recorded in our literature and from the statistics here quoted that the disease is either very rare in the United States or that its presence is unrecognized. Yaws could scarcely be prevalent in the northern part of this country, as it is strictly a tropical disease. It seems evident that the comparatively few cases seen in the northern states are imported from elsewhere. That yaws is more prevalent in the South than is generally supposed is the opinion of Wood, who writes "Since studying the condition more fully I am inclined to suspect that we have been overlooking yaws and that among the negroes the disease has occurred in the South frequently and has been counted as syphilis." Continuing, he says that "every negro is assumed by most writers to be guilty of syphilis until he proves his innocence. Can it be," he adds, "that syphilis is being generally confounded with yaws in this manner and can it explain the well-recognized mildness of present day syphilis among the negro? Surely, we see comparatively few cases of tertiary manifestations among the negro in comparison to that seen in the white man." In a similar vein, McMurran writes that "a great many of the cases that have been diagnosed by the members of our profession may not have been smallpox but the disease I shall briefly describe" (referring to yaws).

An opposing view to the ones here quoted was expressed by Matas, in 1896, who wrote "How rare yaws has become in this country is demonstrated by the records of the Charity Hospital in New Orleans which show that only two cases have appeared in its clinics in the last

nineteen years. That yaws must be a rarity in the Southern as well as Northern states would seem highly probable to me from the paucity of scientific reports in the South.

In an attempt to obtain further information on this subject, I have recently corresponded with a number of dermatologists in the South. Of the ten correspondents who answered a brief questionnaire, only one, Dr. H. E. Menage of New Orleans, had personally seen a case of yaws in the United States. This was a case observed "years ago at the Charity Hospital," which, he wrote, "we took for yaws," and added "if my memory serves me correctly he was a negro, native born." The others who wrote that they had not encountered the disease in this country were Drs. Marcus Haase (Tennessee) J. B. Shelmire, I. L. McGlasson and E. D. Crutchfield (Texas) J. L. Kirby-Smith (Florida) J. H. Edmonson (Alabama) E. P. McGavock (Virginia) C. O. Abernethy (North Carolina) and J. H. Fox (Mississippi). Of these, Dr. Kirby-Smith had formerly studied the disease in the Philippine Islands. He wrote "I am sure I would recognize yaws when seen in my practice." In answer to the question as to whether yaws was at all prevalent in the United States at present, all answered in the negative except one (Dr. McGavock). All who expressed an opinion regarding the former prevalence of the disease (in slavery times) answered in the negative. In this connection, Dr. Haase wrote "I do not think it was prevalent among the slaves as the negroes were excellently cared for at that time because they were valuable property"; an opinion that coincides with my own regarding some other skin diseases in the negro.

The question of the former prevalence of yaws among the negro slaves imported from Africa, particularly in the seventeenth and eighteenth centuries, is purely a matter of speculation. One thing seems certain, namely, that the disease has never gained a foothold and become endemic to any degree in the United States. From his study of the subject, Jones concludes that "the yaws is an African disease and disappears gradually when introduced upon the North American Continent."

Granted that yaws has not obtained a permanent foothold in the southern states, such an occurrence in the future would seem to be within the range of possibilities on account of the prevalence of the disease in neighboring countries. In his volume on the "Geography of Diseases," Clemow [21] says, in regard to yaws, that the West Indies "form one of the most important centres in the world of this disease." According to this writer, it is especially prevalent in Jamaica, Guadaloupe, Martinique, Trinidad, St. Lucia, Grenada, Antigna and Dominica

21. Clemow, F. G.: The Geography of Disease, London, C. J. Clay & Sons, 1903, p. 560.

It appears uncommon in Central America, but is fairly widely distributed in South America. The great prevalence of yaws in Santo Domingo is shown in a recent and most instructive study of 1,046 cases by Moss and Bigelow.[22] During the last two weeks of their stay in the island, the daily number of new and old cases ranged between 100 and 300.

If yaws by some possibility should become endemic in the southern part of the United States, it would not be a great cause for alarm. Though the disease is a most undesirable one, its diagnosis can now be aided by laboratory methods, and its successful treatment by arsphenamin constitutes one of the great triumphs of modern medicine.

CONCLUSIONS

1. Whether yaws was prevalent in the Southern states during the earlier days of slavery appears doubtful. It is a question at all events that can never be settled.

2. Yaws is a rare disease at the present time in the United States, in spite of its great prevalence in certain parts of the West Indies.

3. The majority of the recorded cases have been observed in our northern seaports and have evidently been imported from foreign countries.

4. Yaws would probably never thrive in the northern states as it is purely a tropical disease. With modern laboratory aids to diagnosis, and treatment with arsphenamin, the disease could easily be eradicated if it ever obtained a foothold in the Southern states.

DISCUSSION

Dr. John E. Lane, New Haven: Dr. Fox's reference to the history of yaws in this country reminds me that the Rev. John Clayton, in 1687, referring to Virginia, wrote to Dr. Nehemiah Grew of London as follows: "Among the Indians they have a Distemper which they call Yaws, which is nearly related to the French-Pox; which they are said to cure with an Herb that fluxes them. But this I have only by Hear-say." A description of yaws is given in a book attributed to John Tennant, published in Annapolis about 1730, entitled "Every Man His Own Doctor, or the Poor Planter's Physician." The treatment described in this book is rather interesting. A decoction of sumac root, bark of pine and bark of spanish oak was used for purge and emetic, and in addition two pills made of equal parts of deer's dung and turpentine were to be taken at bedtime.

Dr. William Allen Pusey, Chicago: I think Dr. Fox has done a service to us in giving the facts of this matter in America. It is gratifying that yaws has not obtained a foothold here. This is rather difficult for me to understand, because communication between gulf ports and the West Indies has been very intimate since the settlement of the country; the conditions among the negroes in the subtropical districts along the gulf are very like those in the West Indies, and it is very remarkable to my mind that the disease has not

22. Moss, W. L., and Bigelow, G. H.: Yaws: An Analysis of 1,046 Cases in the Dominican Republic, Bull. Johns Hopkins Hosp. **33**:43 (Feb.) 1922.

obtained a foothold there. This suggests the possibility that there is some other factor in its propagation, which is not included in the ordinary term "tropical climate," because the tropical and other features of the climate of a good part of our gulf border are not unlike those of the West Indies. The only part of Dr. Fox's conclusions that I would be inclined to say is not self-evident is the view that yaws cannot get into this country because it is a tropical disease. I should say rather that the possibility of its communication to this country is exceedingly unlikely, owing to some factor as yet unknown, because it may be some other thing—perhaps the variety of sugar cane or of bananas which these people eat—rather than the climate that is responsible for the disease.

Dr. Charles J. White, Boston: I am sorry to say that I cannot enlighten the association on the great number of cases recorded in Boston. I was entirely unaware of such an occurrence. It was before my day, of course. We cannot account for it in the way of immigration; we do have some inhabitants from the Cape Verde Islands, but, so far as I am aware, they do not have yaws. The man we saw was treated with iodid of potassium and the lesions disappeared very quickly.

Dr. Jay Frank Schamberg, Philadelphia: From the clinical photographs and the histologic pictures shown by Dr. Fox, it is evident that his is a classic case of yaws. The pictures are almost identical with those in the case reported by Dr. Klauder and myself. There are some points of general interest. In the first place, I believe it is beyond the powers of any man to distinguish between *Spirochaeta pallida* and *Spirochaeta pertenuis* under the dark field. But you will find that the field will swarm with spirochetes in yaws; whereas, in the secondary eruption of syphilis, they are sparse. We also found that *Spirochaeta pertenuis* was very difficult to stain with coloring agents that are very quickly taken up by *Spirochaeta pallida*. Another point is the difficulty of perpetuating this infection through successive generations of rabbits. Dr. Klauder succeeded in carrying it through a series of rabbits, but after a time lost it. We sent a strain on to Dr. Nichols of the Army and after a time his strain died out too. It appears to be easier to perpetuate *Spirochaeta pallida* than the spirochete of yaws.

A matter of importance is that, in this disease, we have an infection very strongly resembling syphilis, yielding a strongly positive Wassermann reaction, exhibiting a spirochete difficult to differentiate, and succumbing to the same arsenicals as syphilis. This may readily cause confusion in diagnosing the disease and, by a posteriori reasoning, it may lead to injustice to men enlisted in the Army or Navy. This happened in the case we reported. A soldier in France contracted a disease which was diagnosed as syphilis but which was proved to be yaws. If it had been syphilis, the man would not have been entitled to compensation because the disease would then not have been contracted in the line of duty. I think the diseases are of common origin, but in yaws the spirochete has become attenuated and is readily destroyed. The organisms in yaws appear to be very easily exterminated by a few injections of neo-arsphenamin. They are occasionally found in the spleen. An observation that may shed some light on our obscure comprehension of the significance of a persisting positive Wassermann reaction is this: While there is a very rapid disappearance of the lesions in yaws after one or two injections, the Wassermann reaction does not clear up right away. There is nothing in the literature on this, but in the case studied by us we made tests from week to week, and in spite of the prompt disappearance of the lesions, there was a very slow disappearance of the positive Wassermann reaction.

It was still slightly positive when the patient disappeared from observation. What is the significance of this persisting Wassermann reaction? Does it mean that the arsphenamin treatment killed most of the spirochetes and that those that survived were gradually destroyed by the natural defenses of the body, or does it mean that all were destroyed and that the positive Wassermann reaction was due to the presence of antibodies in the blood? In view of the fact that the statement is commonly made that yaws is cured by one or two injections of one of the arsphenamins, it is urged that the Wassermann reactions in these cases be followed up.

Dr. Charles M. Williams, New York: This case is of interest in connection with the case I presented before the New York Academy of Medicine which was diagnosed syphilid. I think the evidence is correct. The resemblance of yaws to syphilis is exceedingly close; and, if a man is not on the lookout for yaws, the diagnosis is rarely made. Considering how many men treat syphilis and how few think of yaws, there is opportunity for a great leak. There are two points in the diagnosis. The case of Dr. Fox is classic. One special point is the great number of lesions. This is a diagnostic point between yaws and the lesions of syphilis. Very often we think of secondary syphilis as being all over the body, and this is ordinarily the case; but, in my experience, there have been very few lesions in the cases of frambesiform syphilis; whereas, in yaws, there are many. Also, in looking up the literature in my own case, I found that lesions on the scalp and over the forearm are a very common feature in yaws.

Dr. E. L. Oliver, Boston: I should like to say a few words about the case Dr. White reported. I was working under Dr. White at that time, and one of the tests mentioned in the literature of this disease is the lack of sensitiveness of the lesions to acetic acid. In the case reported by Dr. White, I removed the crust covering one of the lesions and then applied 30 per cent. acetic acid, and I found that the lesions were totally insensitive to the acid, although they looked as if they would be very sensitive.

Dr. Marcus Haase, Memphis: It is easy to understand why yaws was not imported to the United States during the time of slavery. The dealers naturally picked the specimens that they brought to the Southern states. These men were placed on the block with nothing more than a strap on, if they were not entirely naked, when they were shown by the auctioneer, and naturally they would not bring one into the country with any such blemishes as yaws would produce.

Dr. Howard Fox, New York (closing): In regard to Dr. Schamberg's remarks concerning the profusion of spirochetes seen by the dark-field illumination, this was apparent when our examinations were made. I do not feel that the average observer could possibly distinguish morphologically between *Spirochaeta pallida* and *Spirochaeta pertenuis*. That the organisms, as Dr. Schamberg mentioned, have been found in the spleen, is true, but they do not seem able to obtain a foothold in this or other internal organs and produce any damage. It does not seem probable that yaws could become endemic in temperate climates. Up to the present time, it has been a strikingly tropical disease, and it has been said that in the tropics it is not encountered at an elevation higher than 800 feet. Dr. Williams' suggestion that many cases are overlooked is perfectly plausible. The disease in the United States must either be rare or unrecognized. It seems unlikely that yaws is really prevalent considering the present large number of well trained dermatologists scattered over different sections of the United States.

114 East Fifty-Fourth Street.

EROSIO INTERDIGITALIS BLASTOMYCETICA*

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Saccharomycetic infections of the skin have long been recognized, but only recently has the subject been given the attention that it merits. Among the earlier studies were those of Gougerot and Goncea,[1] who described saccharomycetic organisms which they had isolated from lesions on the hands and feet. In our[2] paper on ringworm of the extremities, we mentioned the finding of a similar organism which was encountered in three cases. In our later work on mycotic infections of the hands and feet the yeast was grown from time to time, but as we were concerned with *Epidermophyton inguinale* and other related fungi, the yeast was disregarded.

In May, 1917, Fabry[3] described a series of yeast infections of the hand, to which he gave the name *Erosio interdigitalis blastomycetica.* In 1918, Berendsen[4] published an inaugural dissertation on the same subject. In 1918, Fabry[5] published another paper, and in April, 1921, Stickel[6] reported a series of forty-five cases, thirty-eight of which occurred in women. In March, 1922, Greenbaum and Klauder[7] made a valuable contribution to the subject of yeast infection.

The cases described by the German authors are all characterized by the appearance of a benign, superficial, well-defined, red, shiny lesion situated on the web of the finger, usually in the third or fourth interspace. In Stickel's series of cases there were thirty-eight women and only seven men. The disorder was never encountered in children. It is most commonly seen in women who wash clothing or have their hands in water in the course of housework. Soap suds seems particularly to be a causative factor in the production of the disorder or at

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* Read at the Forty-Fifth Annual Meeting of the American Dermatological Association, Washington, D. C., May 2-4, 1922.

1. Gougerot and Goncea: Bull. Soc. franç. de dermat. et de syph., July, 1914; December, 1915, p. 335.

2. Ormsby, Oliver S., and Mitchell, James Herbert: Ringworm of Hands and Feet, J. A. M. A. **67**:711 (Sept. 2) 1916.

3. Fabry: München. med. Wchnschr., 1917, No. 48, p. 1557.

4. Berendsen: Inaugural Diss., Berlin, 1918.

5. Fabry: Weitere Mitteilungen über Erosio interdigitalis blastomycetica, Dermat. Wchnschr. **66**:321 (May) 1918.

6. Stickel, J.: Dermat. Wchnschr. **72**:257 (April 2) 1921.

7. Greenbaum, S. S., and Klauder, Joseph V.: Yeast Infections of the Skin: Report of Cases and of Studies on the Cutaneous Yeasts, Arch. Dermat. & Syph. **6**:332 (March) 1922.

Fig. 1.—Appearance of hands when first seen in August, 1921.

Fig. 2.—Appearance of hands in January, 1922.

Fig. 3.—Appearance of hands at present time.

least in the continuance of the infection. Neither vesication nor lymphangitis was observed in any of the cases. In only one case did the infection spread over the volar surface.

Examination of the squames with potassium hydroxid in the usual way disclosed double contoured yeastlike spores. Inoculation of the interdigital surfaces with the pure culture of the organism was successful in seven cases. Subcutaneous injection of the organism in white mice caused a formation of abscesses with local alopecia.

Greenbaum and Klauder report, among their other cases, seven cases of the interdigital type yielding pure culture of yeast. The authors made a careful study of the different types of yeast organisms and divide them into four groups. Greenbaum and Klauder also successfully produced a typical lesion by inoculation of the pure culture.

Fig. 4.—Cultures of yeast organism.

My own observations were made in three cases seen in dispensary practice; two of these patients disappeared after the first visit and were lost to view. All three patients were women who were doing heavy housework. The third case has been under constant observation since August 10, 1921, and was demonstrated at the January meeting of the Chicago Dermatological Society.

REPORT OF CASE

History.—The patient was an untidy Jewish woman, 26 years of age, who weighed 300 pounds. She had been married twice, and owing to nonsupport by her second husband, she had been washing clothes for a living. The lesions first appeared six years before on the web of the third interspace on either hand. They had been present constantly since the onset six years before, with only an occasional slight remission. The lesions had remained constantly in the same areas and had shown no tendency to spread either to the dorsal or to the palmar surfaces.

According to the statement of the patient, there was never any vesication before coming under observation, and since August, 1921, there had been no suggestion of vesicle formation. There was a moderate amount of itching and burning which was intensified by having the hands in soapy water.

Examination.—The lesions consisted of well-defined areas of shiny red epidermis surrounded by a collarette of upturned scales. Here and there were small areas of white macerated thin epidermis which could be removed only with a great deal of difficulty and much discomfort to the patient. In cold weather a fissure was occasionally seen in the center of the lesion on the dorsal margins.

Fig. 5.—Double contoured yeast organism.

At no time had the lesions spread beyond the opposed surfaces of the web of the third and fourth fingers. The feet were free from any suggestion of mycotic infection.

Microscopic Examination.—Examination of the very small pieces of tissue which could be removed with difficulty disclosed double contoured spores which were budding here and there. There were also numerous mycelial threads which appeared to be solid rather than made up of segments, as is the case with *Epidermophyton inguinale*. There were also here and there spores which lacked the double contour and which showed no signs of budding. Plants of the tissue on Sabouraud's proof medium had given rise to creamy, white, shiny colonies

of yeast organisms which microscopically were seen to be double contoured and to be budding quite freely. The colonies appeared three to five days after implantation, and when the culture attained a size of about 3 cm. the colony ceased to extend peripherally. Owing to the extreme intractability of the disorder to treatment, no attempts were made to inoculate the organisms on the hand of this or other patients.

Treatment and Course.—The treatment consisted at first in the use of Whitfield ointment in the usual strength. This apparently had no effect and was abandoned. Later chrysarobin in both chloroform solution of gutta percha and petrolatum was used, but likewise without effect.

Radiotherapy was then administered, but despite all the radiotherapy that was deemed safe the lesions persisted apparently unchanged. The treatment tried by Stickel, consisting of the application of a weak tincture of iodin night and morning and the rubbing on four or five times during the day of 20 per cent. salicylic acid powder, was carried out, but this likewise was without effect. As the patient was obliged to wash clothes she had her hands in water constantly. Aid from the United Charities finally enabled her to give up washing for a time, and apparently the discontinuance of laundry work was the only thing that was of any value in the management of the case.

The term erosio interdigitalis blastomycetica is confusing as it leads to the supposition that the causative organism is the well-known blastomyces, with which it has nothing to do. Substitution of saccharomycetica for blastomycetica would be advisable.

The chronicity of the disorder, the fixed location of the lesion, the absence of vesication, the resistance to therapy and the occurrence of the disorder on the hands of washer-women, make the dermatosis worthy of consideration as an entity.

Whether or not the yeast is the causative organism I am not prepared to say, as I have carried out no inoculative experiments, for the reasons given in the foregoing.

MALIGNANT ENDOTHELIOMAS WITH CUTANEOUS INVOLVEMENT *

A CLINICAL AND HISTOPATHOLOGIC STUDY WITH A REPORT OF THREE CASES

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The rarity of occurrence, the peculiarities of the clinical course, and the fact that the true nature of the tumor is often concealed because of early surgical or medical interference make a malignant endothelioma peculiarly difficult to distinguish by its clinical characteristics. Because of the difference of opinion regarding the actual existence of endotheliomas, and because of the possibility of serious diagnostic error, illustrated by our own experience, I shall discuss malignant endothelial tumors in the light of three cases which clinically and histopathologically appear to aline themselves with this group.

The variability of the endothelial cell in neoplasms and the ability of endothelium to undergo metaplasia, simulating the epithelial type at one point and the connective tissue type at another, has given rise to confusion in the differential diagnosis of endothelial tumors. The controversy with regard to the actual existence of endothelial tumors and the criteria for diagnosis is, in part, due to the difficulty of obtaining material from the primary focus at a point where the structure still shows that undoubted endothelial cells gave rise to the tumors. Because of the relatively slow onset and low grade of malignancy of tumors from cells lining blood vessels, lymph vessels, lymph spaces, and serous surfaces, the neoplastic change is usually well advanced before a diagnosis is even attempted. The size of the growth at the time of study makes it practically impossible to trace the various cells through their transition stages to the original proliferating endothelium. This point, among others, is illustrated by the first case [1] of my series.

REPORT OF CASES

CASE 1.—*History.*—J. C., a man, aged 34, was first examined at the Clinic, April 10, 1921. He had a large ulcer on the left forearm (Fig. 1). His general

* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Dermatology and Syphilology, April, 1922.

1. This case was presented for diagnosis by the Section on Dermatology and Syphilology of the Mayo Clinic before the joint meeting of the Minnesota, Chicago and St. Louis Dermatological Societies at Rochester, Minn. August, 1921

health had been good, except for the lesion described, up to the time of his first examination in the Clinic. Thirteen years before he had been kicked on the forearm by a mule, but the arm had not been fractured, and little swelling or soreness had resulted. A few days later, he had noticed a small lump on the forearm about 5 mm. in diameter, which had gradually increased to 1.5 cm. in diameter within a year. He had had practically no pain. In 1914, five years after the onset of the lesion, the nodule, which had grown to be about 2 cm. in diameter but had not broken down, had been surgically removed. The mass had recurred in situ, and a year later, April, 1915, a second operation was performed. An infiltrated mass which extended from 7.5 cm. above the wrist to within 7.5 cm. of the elbow had been removed leaving a large granulating surface which had healed partially. In October, 1915, the lesion had again been explored and cauterized. Following this operation the wound had remained open and had given off a continuous bloody discharge. At no time had there been much pain or tenderness, a remarkable fact in view of the size and nature of the lesion.

Fig. 1 (Case 1).—Large ulcer on forearm.

From October, 1915, to the date of admission to the Clinic the patient had received intensive local and systemic treatment without benefit. The treatment consisted of six intravenous injections of arsphenamin, twelve intramuscular injections of mercuric salicylate, potassium iodid by mouth, two exposures to radium of two hours each, the number of milligrams not known, violet and roentgen-ray exposures, various antiseptics including a surgical solution of chlorinated soda, continuous wet dressings, and continuous local baths. The patient did not give a history of syphilis, and the blood Wassermann reaction had always been negative.

Examination.—The ulceration extended from 7.5 cm. above the wrist to within 5 cm. of the elbow. The borders were irregular, indurated, undermined, reddish to purple and markedly hemorrhagic. Along the upper margin the border was slightly rolled and "pearly." The arciform configuration suggested a syphilitic lesion. The ulna was exposed, and although there was no evidence of periostitis, the bone was necrosed, the shaft being partially destroyed. The extensors of the thumb and finger were destroyed. The elbow and lower third of the arm were swollen. A mass was palpable in the axilla, and cordlike lines of infiltration extended from the broken down tissue to the elbow

flexure. There was also a nodule higher on the brachial lymphatics, with slight diffuse infiltration of the surrounding skin. There was tumid induration of the tissues above the lesion.

In investigating the possibility of syphilis seven Wassermann reactions on the blood following a provocative injection of 0.3 gm. of arsphenamin were made, biopsy was performed, and cultures were taken; the provocative series of reaction was negative, the biopsy demonstrated subepithelial fibrosis with inflammatory changes, and the culture revealed an acid-fast bacillus.

Treatment.—On the hypothesis that the lesion might be an infectious granuloma allied to granuloma inguinale tropicum, the patient was given ten daily injections of from 3 to 10 c.c. of a 10 per cent. solution of tartar emetic. Local wet dressings of a 1:4000 solution of potassium permanganate, were used, and the lesion was exposed three times to rays from an Alpine sun lamp. The lesion became less hemorrhagic, and there was less odor and sloughing. The edges of the ulcer were then painted with a 5 per cent. scarlet-red ointment, and the base with a 10 per cent. solution of balsam of Peru. An aluminum

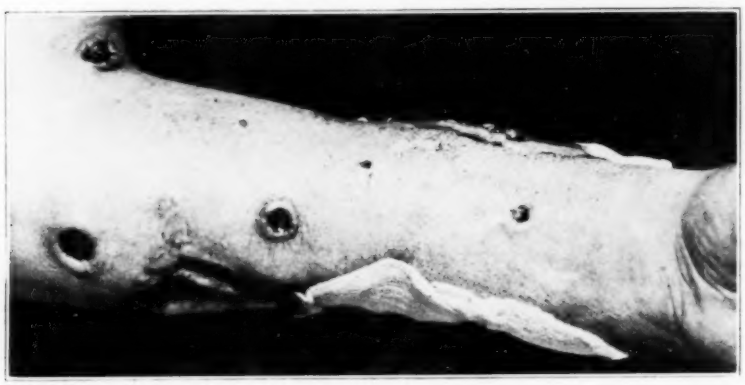

Fig. 2 (Case 1).—New nodules which developed and broke down while the patient was under observation.

acetate wet dressing was used. During the following three weeks an abscess slowly developed in the left axilla. Cultures from aspirated pus showed short-chain streptococci. Three days after drainage a profuse hemorrhage occurred from the axillary wound, and blood transfusion was performed. The lesion on the forearm continued to improve slowly under the local treatment, and July 30 a second biopsy was performed. The sections revealed a vascular, inflammatory, granulomatous tissue, with marked plasma cell infiltration around the vessels, inflammatory muscle tissue, fibroblastic strands and septums, no giant cells, no bacteria and no epithelial change except a moderate degree of acanthosis. The lesion was then regarded as a granuloma of unknown type, and treatment for syphilis was again resorted to. The patient was given six intravenous injections of arsphenamin at weekly intervals in conjunction with twenty intramuscular injections of mercuric succinimid, one-sixth grain (0.01 gm.), without local improvement. Following this treatment radium was used on the nodules in the axilla and upper arm, and the lesion in the forearm was exposed to the roentgen ray. October 15, six months after the patient was first seen in the Clinic, Dr. Stokes suggested the possibility of new light

on the diagnosis by the removal of a small new nodule near the older lesion (Fig. 2). This material was examined microscopically by Broders and diagnosed as endothelioma. The importance of obtaining a specimen from an early nodule was demonstrated, for in two previous biopsies on the border of the old ulcer only a vascular structure with inflammatory change (granuloma) was revealed, and there was no evidence of the true character of the original process. After the diagnosis of endothelioma was made, the arm was amputated at the juncture of the middle and lower third of the upper arm. A small nodule from the inner side of the upper third of the arm was excised. The sites of possible metastasis were then repeatedly exposed to the roentgen ray and radium until the patient was dismissed, apparently in good health.

Histology.—The histologic structure of the fresh nodule in this case was, on first examination, rather unusual and complex. The most striking features, when viewed with the low power lens, were an undifferentiated polymorphic cell type of growth, a whorl arrangement of the cells, the formation of elongated cellular

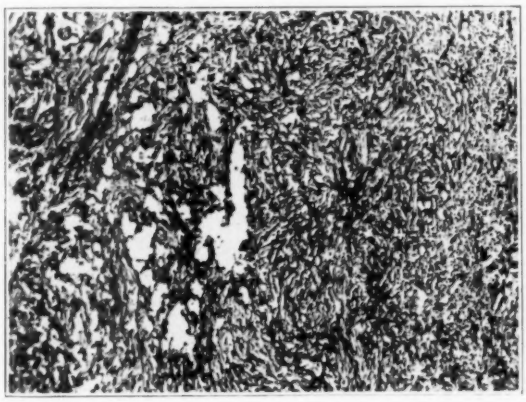

Fig. 3 (Case 1).—Section from a new nodule having the two characteristic structures of the tumor: a solid area with cells arranged in whorls, and an area of more advanced differentiation into vascular structures, × 50.

strands and narrow trabeculae, and the close association of the tumor with blood vessels and the formation of channels which might contain blood cells (Fig. 3). Many of the cell strands or trabeculae, when studied with higher magnification, appeared to be essentially ingrowths from or proliferations of the endothelial lining of the blood vessels and blood spaces. The cellular ingrowths by constant proliferation first formed the solid or whorled masses of cells; then vacuolization of the individual cells in the clumps and solid masses occurred with the formation of loose trabeculated areas and an attempt at differentiation into capillaries and blood spaces. The individual tumor cells were, in general, larger than normal endothelial cells, but they varied enormously in size and shape, having no typical form. Oval, cuboidal, spherical, flattened, and long columnar forms occurred, but the majority were spheroidal. In certain areas, syncytial or branching forms were seen which resembled the true vasoformative type of cell. These cells suggested the true nature of the growth. There were neither characteristic tumor cells nor foreign body giant cells. A constant feature of the tumor was the occurrence of what appeared to be

vacuoles in the cytoplasm of practically all cells. These vacuole-like areas which did not take stain, and which apparently did not contain fat, glycogen, hyalin, or colloid material, were of great importance, for by their confluence the lumina of the large characteristic sinuses and channels were formed (Fig. 4). In the solid areas composed of whorls of cells, the vacuoles of the individual cells were small, but they showed evidence of coalescence to form larger spaces (Figs. 5 and 6). In less dense portions of the neoplasm, vacuoles displaced almost the entire cytoplasm of the cells, and by their confluence formed much larger spaces. These parts of the tumor represented, apparently, an attempt at differentiation into vascular structures. This differentiation, however, was incomplete, and these spaces at best represented only rudimentary capillaries and blood spaces. In the walls, the tendency of the cells to exhibit their true nature was easily seen. The cells bordering on these spaces arranged themselves in rows, became elongated, and formed a rudimentary endothelial

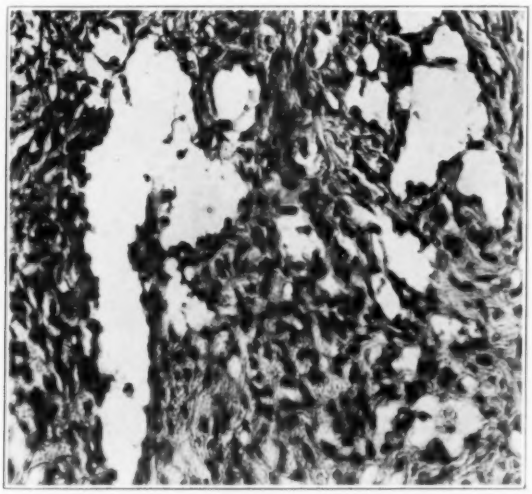

Fig. 4 (Case 1).—Tumor cells form trabeculae; vacuoles in the cytoplasm of individual cells; the coalescence of these vacuoles forms large spaces, × 160.

lining of the spaces. The cells were thicker than normal endothelium, however, and the lining usually consisted of several layers, although in some it might have consisted of a single layer, or might have been absent altogether (Fig. 7). These lining cells also expressed the character of the tumor by the formation of new vacuoles in the cytoplasm. There was a suggestion of further proliferation of the lining with the formation of new cellular ingrowths into the newly formed spaces themselves.

The sinuslike spaces were occasionally filled with erythrocytes which, apparently, had been extravasated, following the rupture of true blood vessels in the vicinity (Fig. 8). There was no evidence of circulation; neither could connection between these spaces and the true circulation be demonstrated. The individual tumor cells had nuclei which were extremely variable in shape and larger than the nuclei of normal endothelial cells. Occasionally multinucleated cells could be found, but no mitotic figures. A delicate intercellular cement could often be distinguished. In certain regions free infiltration into the muscle

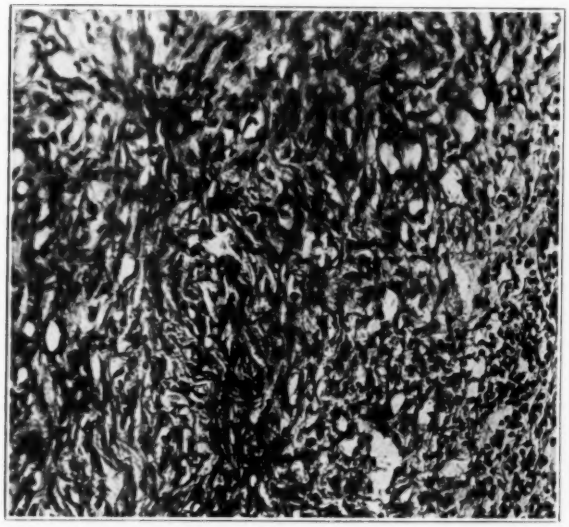

Fig. 5 (Case 1).—Early stages of vacuole formation, × 160.

Fig. 6.—Various types of cells with vacuoles in the cytoplasm, × 500.

tissue of the surrounding part was demonstrable, and isolated muscle fibers were surrounded by tumor cells. There was moderate round-cell infiltration. No involvement of the overlying epidermis was apparent. There was, however, moderate acanthosis. Slight plasma-cell infiltration around the vessels occurred even in the early noninflammatory nodule.

Case 2.—*History.*—C. M., a woman, aged 24, came to the Clinic because of an ulcer on the left heel. At the age of 7, she had had a furuncle over the left Achilles tendon, and later an abscess on the same leg just below the groin. Ten years before, in 1900, a nodule had developed on the inner side of the left heel. In 1906, the nodule had ulcerated and had begun to discharge. Four operations had been performed without benefit, and contracture of the Achilles tendon had resulted. Since 1908, the patient has had severe hemorrhages from the bowels at intervals of about six months.

Examination.—Proctoscopic examination of the lower bowel was negative. A biopsy of the ulcer on the heel was performed, and the diagnosis was sarcoma

Fig. 7 (Case 1).—Cells bordering the spaces arrange themselves in rows to form an endothelial lining for the space, × 500.

or endothelioma. The lesion was cauterized and packed, but there was recurrence, and a second operation was performed, Nov. 30, 1910. Again, the lesion recurred and was operated on, Jan. 20, 1911. Microscopic examination again revealed malignant growth. A specimen removed, Feb. 23, 1911, presented the pathologic picture of oval-cell sarcoma. March 3, 1911, a new nodule which had developed on the ankle, the ulcer on the foot and the left inguinal glands were removed, and the cautery was used. Specimens from all of these areas presented the same pathologic picture. The patient went home, and Nov. 14, 1912, in reply to an inquiry, said she had recurrent lesions at the former sites, and also five small tumors in various other parts of the body. She did not return for further examination or treatment, and died, May 4, 1913, three years after examination in the Clinic, and thirteen years after the first apperance of the lesion.

Histology.—The histopathologic findings in the lesions from this case varied considerably according to the time and place of removal of the specimens.

Here too a polymorphic-cell, undifferentiated type of growth (Fig. 9), was found. The cells at certain points in the tumor had a whorl arrangement, and at other points were arranged in ropes or cords with the formation of trabeculae. There was no close association with blood vessels. With high magnification, the cell strands and cell masses appeared to have the characteristics of endothelium. The cells in general, however, were larger than ordinary endothelial cells. They varied in shape from spheroidal to cuboidal. Giant cells were not demonstrable. An occasional dividing cell and mitotic figure were seen. The conspicuous and constant feature was the occurrence of vacuoles in the cytoplasm of the cells, which tended to coalesce with the formation of spaces and channels. The cells lining these spaces were flattened, and had taken on the character of true endothelial cells (Fig. 10). Erythrocytes were found in a few of these spaces, but as in Case 1 no connection with the true circulation could be demonstrated. The vacuolization, however, and the attempt at differentiation into vascular structures were much less evident

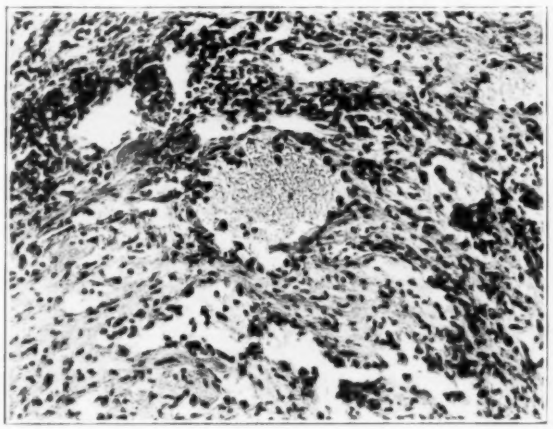

Fig. 8 (Case 1).—Red blood cells in newly formed sinuses, × 100.

than in the former case. The nuclei of the individual cells were large, and extremely variable in size and shape. Only a delicate intercellular substance was present. There was free infiltration into the surrounding tissues. Examination of the overlying epidermis did not reveal a lesion. The tumor merged into surrounding highly vascular granulation tissue (Fig. 11). Specimens from the heel, ankle, and groin exhibited the same characteristics, but in different degrees.

Case 3.—*History.*—O. W. C., a man, aged 26, one year before had received a slight injury to the hand in cracking a nut. A small growth without pain or soreness had appeared. Ten months later, a glandular enlargement developed on the right side of the neck which grew to be 3.5 cm. in diameter. Examination revealed besides these nodules an enlarged gland in the right axilla. Both nodules were removed surgically.

Histology.—Microscopic examination of both tumors revealed almost identical pictures. The low power lens showed a cavernous type of growth, in parts of which the cells were whorled or solid (Fig. 12). In the cavernous areas the

cells were arranged in strands with the formation of trabeculae. The individual cellular elements varied considerably in shape and size, but the occurrence of vacuoles in the cytoplasm was a common feature. It was clearly demonstrated that the larger cavernous spaces were formed by the coalescence of these vacuoles. The cells lining the lumina or spaces were flattened out with the formation of endothelium. The occurrence of the large spaces lined with flattened endothelial cells represented a more advanced attempt of the tumor to differentiate into vascular structures than in Cases 1 and 2 (Fig. 13).

DISCUSSION OF THE HISTOPATHOLOGIC AND CLINICAL PICTURES

In Case 1 six months elapsed, during which time the patient was under observation in the Clinic, before the true character of the tumor was discovered. The distorted picture at the first examination made it

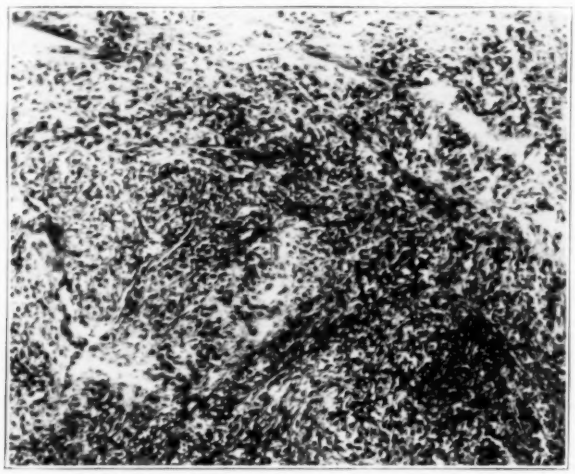

Fig. 9 (Case 2).—The polymorphic cell, undifferentiated type of growth in tumor on the ankle. In certain areas differentiation into sinuses is beginning. × 75.

almost impossible to recognize the character of the growth either by inspection or microscopic study. The history of a tumor of thirteen years' duration without definite metastasis suggested a benign rather than a malignant growth. No evidence of the original character of the lesion remained in the large ulcer. Repeated biopsies on the border of the lesion did not show a tumor of endothelial origin. In its place was a granuloma, probably the product of chronic infection. An imperfectly arciform configuration suggested the possibility of syphilis rather than malignancy. This was considered improbable, however, because of the inability of serologic confirmation, and the failure of the lesion to respond to treatment for syphilis. The distorted clinical picture is explainable on the ground that the lesion had been subjected

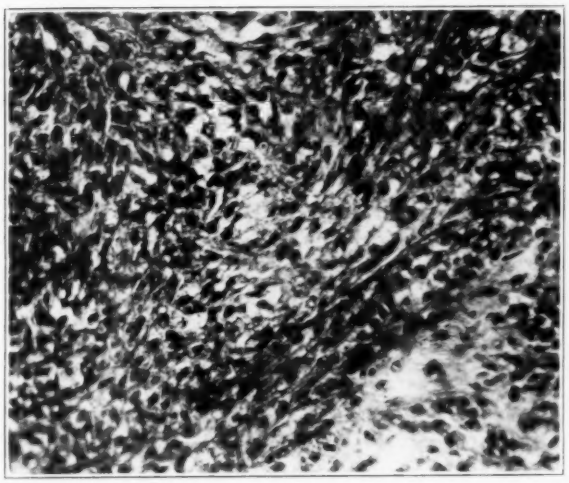

Fig. 10 (Case 2).—Vacuole formation in practically all cells, × 150.

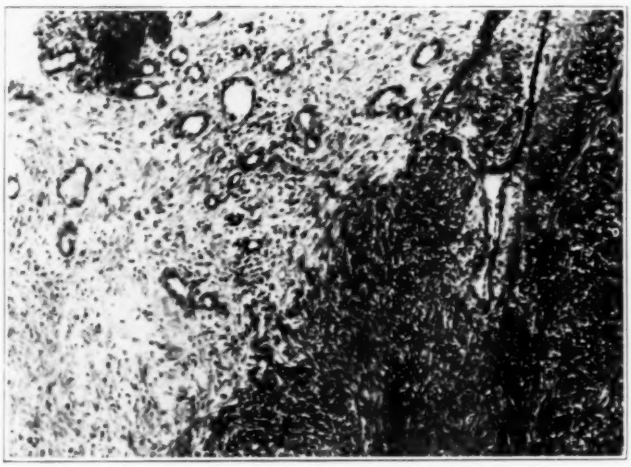

Fig. 11 (Case 2).—Characteristic masses of tumor cells closely associated with surrounding highly vascular granulation tissue, × 75.

to repeated surgical interference and that, to a large extent, secondary pyogenic infection was present, as evidenced by the purulent discharge and the metastatic abscess in the axilla. A culture from the lesion revealed a gram-negative bacillus, probably saprophytic. The response of the lesion, and the improvement in the general health of the patient under local medication, is explained by the fact that the local infectious process was partially controlled. There was no effect, however, on the original neoplastic element, as evidenced by the occurrence of new nodules in the upper and lower arms. In Case 1 the original tumor was almost completely replaced by a secondary condition. In retrospect,

Fig. 12 (Case 3).—Cavernous structure characteristic of this tumor, × 50.

the hemorrhagic character of the tumor, the relatively benign course of the lesion, the good general condition of the patient, the long delayed metastasis, which did not occur until the tumor had reached considerable size, and the appearance of the original lesion at a site of trauma might have led one earlier to suspect malignant endothelial tumor.

Cases 2 and 3 presented clinical pictures in many ways similar to Case 1. Common features of both were the hemorrhagic character of the lesion, the onset following trauma, the relatively benign course of the growth, the late metastasis and the good general health of the patients. Histologically the tumors in the three cases presented essentially the same picture. These three tumors, because of the infiltrative and destructive growth and metastasis, must be regarded as

malignant growths. Should they be designated as endotheliomas, even though they reproduce the structure of the hyperplastic endothelial cell?

The inability to obtain an early nodule showing the actual beginning proliferation of the endothelial cells makes it, of course, difficult to demonstrate that cells of undoubted endothelial origin give rise to the cell masses. However, the tumor cells, in general, exhibit so many characteristics of the endothelial cell that it seems justifiable to designate them as such. The undifferentiated, polymorphic-cell type of growth, the appearance within the cells of vacuoles which in turn coalesce to form the rudimentary blood spaces, the syncytial or branch-

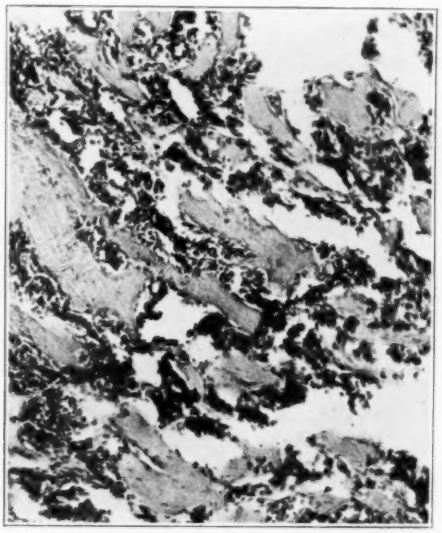

Fig. 13 (Case 3).—Section from metastatic nodule showing the same cavernous structure as the parent tumor, × 75.

ing forms which resemble the true vasoformative type of cells, and the differentiation of the cells lining the newly formed spaces into fairly typical endothelium, are all constant features which suggest endothelial origin. In Case 2 the differentiation into capillaries and spaces was the least complete, and the tumor from its clinical behavior was the most malignant. In Case 1 the differentiation was more advanced and malignancy less marked. The tumor in Case 3, however, showed almost complete differentiation into vascular structures and, to judge from its clinical behavior, was least malignant. It seems evident, then, that the malignancy of the tumor depends, in part, on the degree of differentiation as in other neoplasms, the differentiation in this case being into vascular structures.

THE CLASSIFICATION OF ENDOTHELIAL NEOPLASMS

According to Ziegler,[2] Delafield and Prudden,[3] MacCallum,[4] and others, the classification of tumors depends on whether their growth is typical or atypical, on their morphology and on their histogenesis. Two tumors may be the same morphologically and histogenetically, but one may be benign and the other malignant, depending on whether or not it is a typical or an atypical growth. Carcinoma is an atypical growth of epithelial origin. It is a malignant tumor derived from tissues which have their origin in the ectoblast or entoblast, the only exception being the lining of the genito-urinary tract whose epithelium, as far as the bladder, is of mesoblastic origin, and hence genetically closely related to the extensive mesoblastic group of tissues. In the same way, a sarcoma is an atypical growth of connective tissue origin. It is a malignant tumor of structures which are products of the mesoblast. Carcinoma and sarcoma differ in both their morphology and their histogenesis. Their atypical growth characterizes them as malignant. According to Böhm, Davidoff and Huber,[5] Prentiss,[6] and others, the cells which constitute the endothelium that lines the serous surfaces, including those of the pericardium, pleura, dura and peritoneum, with those of the blood and lymph vessels and lymphatic spaces throughout the body, are modified cells of mesoblastic origin. The endothelial cell belongs to the connective tissue group, and is properly regarded as a modified element of that type of tissue. Endothelial cells resemble, however, those of squamous epithelium in that they are markedly flattened with faintly granular protoplasm, possess flattened, oval or nearly round nuclei, are of polyhedral shape, and are united into a single layer by a small amount of intercellular cement substance; although the borders of the cells may be quite regular or slightly wavy, more often they are serrated. The quantity of intercellular cement substances between endothelial cells is so small and the cell boundary so indistinct that it is necessary to resort to special staining methods in order clearly to bring out their outline. On the other hand, in the connective tissues it is the intercellular substance and not the cells that characterize the tissue, the cellular elements themselves forming

2. Ziegler, E.: General Pathology, Ed. 11, New York, William Wood & Co., 1908. pp. 419, 425.

3. Delafield, F., and Prudden, T. M.: A Text Book of Pathology, Ed. 10, New York, William Wood & Co., 1914.

4. MacCallum, W. G.: A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1919, p. 904.

5. Böhm, A. A.; von Davidoff, M., and Huber, G. C.: A Text-Book of Histology, Philadelphia, W. B. Saunders Company, 1900, pp. 84-85.

6. Prentiss, C. W.: A Laboratory Manual and Text-Book of Embryology, Philadelphia, W. B. Saunders Company, 1915, pp. 45, 64.

the less conspicuous portion (Prentiss,[6] Boehm, Davidoff and Huber,[5] Piersol, and others).

An endothelioma, according to the interpretation which is placed on the morphology and histogenesis of the endothelial cell, may be either a tumor of mesoblastic or connective tissue origin (histogenetically a sarcoma), or it may be a tumor composed of cells resembling epithelium (morphologically a carcinoma). The material available in the cases here presented does not permit a decision of this interesting question. The term endothelioma must then stand essentially as a name representing a compromise between the histogenetic and the morphologic views of the classification of tumors. The endothelioma is histogenetically of mesoblastic or connective tissue origin, but morphologically its cellular unit most closely resembles the epithelial cell of ectodermic or entodermic origin which is characteristic of the carcinomas.

THE LITERATURE

There has been much doubt regarding the actual occurrence of endotheliomas. Maurer,[7] in 1879, described two cases of malignant tumors of slow growth composed of ingrowths from the endothelial lining of blood vessels. The tumors exhibited hemorrhagic tendencies and also metastasized. Microscopic examination showed cell masses arranged in whorls and trabeculae which grew by infiltration into and around nerves, ligaments and muscles. Many small round cells with large nuclei were present. The cytoplasm showed a tendency to disintegrate with the formation of vacuoles. By the coalescence of these vacuoles distinct channels and blood spaces were formed, some of which contained erythrocytes. Because of the tendency toward capillary and sinus formation, he called the tumors angiosarcomas. In 1890, Franke [8] described a tumor 11 cm. in diameter, of five years' duration, consisting of tissue and blood spaces lined by endothelial cells in which could be seen what he called hyalin deposits resembling vacuoles. The tumor was formed in the lumen of a vessel from its endothelial lining. He, therefore, suggested the name endothelioma rather than the former name sarcoma. Limacher,[9] in 1898, described a tumor of the thyroid in which there was a distinct attempt at capillary formation. The cells of the tumor appeared to develop from the lining of blood vessels.

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7. Maurer, F.: Ein Beitrag zur Kenntniss der Angiosarcome, Arch f. path. Anat. u. Physiol. **77**:346-363, 1879.

8. Franke, F.: Beiträge zur Geschwulstlehre: Endotheliome intravasculare hyalogene der Submaxillargegend, Arch. f. path. Anat. u. Physiol. **121**:465-482, 1890.

9. Limacher, F.: Ueber Blutgefässendotheliome der Struma mit einem Anhang über Knochenmetastasen bei Struma maligna, Arch. f. path. Anat. u. Physiol., suppl., pp. 113-150, 1898.

Krompecher,[10] in the same year said, "Tumors of the testicle of epithelial character (adenoma and adenocarcinoma) seldom have the histogenesis of epithelium." He believes that testicular tumors other than of epithelial origin usually develop from lymphatic endothelium, but occasionally from connective tissue. He asserts that the origin of lymphendotheliomas in the large lymph spaces has been demonstrated to be from endothelium; the origin of those developing from the lymph vessels had not been definitely proved to be from endothelium but evrything suggested endothelial origin. The term endothelioma characterized the tumor histogenetically and angiosarcoma morphologically. His statement that it is difficult to demonstrate that the tumors in blood and lymph vessels are directly of endothelial origin, although their structure strongly suggests it, is entirely in accord with my observation. Harris,[11] in 1893, mentioned a case of primary cylindrical cell endothelioma of the pleura. In 1895, Volkmann[12] in discussing endotheliomas, characterized them as tumors originating from the endothelial lining of blood vessels, lymph vessels and spaces, and pleural and peritoneal serous surfaces. He asserts that the vacuole-like appearance is due to deposits of glycogen in the cytoplasm, as opposed to the idea of former writers on hyalin degeneration. The vacuoles or spaces in the tumor cells in the three cases of my series apparently contained neither hyalin nor glycogen. Barth,[13] in 1896, differentiated endothelial tumors from carcinoma and sarcoma in that they were new growths with the histogenesis of a fibroma or sarcoma and the morphology of endothelial structures. The case he described was that of a tumor composed of minute capillaries and blood spaces. The endothelial cells were thickened and contained large nuclei. Vacuole formation was a common occurrence in the cell cytoplasm. He traced the origin to a definite proliferation of the endothelial cells of lymph vessels and lymph spaces. Borrmann,[14] in 1898, and Marckwald,[15] in 1899, reported cases

10. Krompecher, E.: Ueber die Geschwülste, insbesondere die Endotheliome des Hodens, Arch. f. path. Anat. u. Physiol., suppl. **151**:1-65, 1898.

11. Harris, T.: A Contribution to the Pathology and Clinical Features of Primary Malignant Disease of the Pleura, J. Path. & Bacteriol. **2**:174-189, 1893-1894.

12. Volkmann, R.: Ueber endotheliale Geschwülste, zugleich ein Beitrag zu den Speicheldrüsen- und Gaumentumoren, Deutsch. Ztschr. f. Chir. **41**:1-180, 1895.

13. Barth, T.: Ein Fall von Lymphagiosarkom des Mundbodens und Bemerkungen über die sogenennten Endothelgeschwülste, Beitr. z. path. Anat. u. z. allg. Path. **19**:462-496, 1896.

14. Borrmann: Ein Blutgefässendotheliom, mit besonderer Berücksichtigung seines Wachstums, Arch. f. path. Anat. u. Physiol., suppl. **151**:151-194, 1898.

15. Marckwald: Ein Fall von multiplem, intravasculärem Endotheliom in den gesammten Knochen des Skelets (Myelom, Angiosarcom), Arch f. path. Anat. u. Physiol. **141**:128-152, 1895.

of endotheliomas of the scrotum and bone. The latter does not say that he was able to demonstrate their origin from endothelium, but their structures suggested such origin.

From 1900 to 1905, opinions differed with regard to the occurrence of endotheliomas, and the definite identity of this group. Wolters,[16] in 1900, reported the case of a patient with nodules of endothelial structure on the chest. Warthin,[17] in 1901, reported a case of a tumor of the parotid which consisted of an overgrowth of the endothelial cells of the lymph spaces, lymph vessels and capillaries. The spindle-shaped cells were directly traceable to endothelium through all their transition stages. Colmers,[18] in 1902, described a nodule in the penis with metastasis in the lymph glands, lungs and pericardium. Histologically, a proliferation from the endothelial cells lining the cavernous spaces of the penis had occurred. Burkhardt,[19] in the same year, said, "Histogenetically one cannot differentiate sarcoma from endothelioma," and he suggested that the term endothelioma be dropped. He believes that if a tumor morphologically resembles endothelioma it should be called a sarcoma-endothelioma. He says that tumors of the same histogenesis may differ in morphology, and that the morphology does not determine the type of the original cell. According to Burkhardt, sarcomas are derived from the various cells which form connective tissue. In the purest and least modified type of sarcoma, the spindle-cell type, there is a definite participation of the endothelium of the lymph spaces. In such tumors the predominating type of cell and the endothelial cells respond to the same stimulus, but in a different degree.

Lazarus-Barlow,[20] in 1903, in discussing the status of endotheliomas held that the term includes a class of tumors which, ontogenetically, belongs to the class of sarcoma, and yet, so far as histologic character is concerned, bears a close resemblance to carcinomas. He says that these tumors are composed of cells having the characteristics of endothelium, and as a result they must originate in structures in which these

16. Wolters, M.: Haemangioendotheliome tuberosum multiplex und Haemangiosarcoma cutis, Arch. f. Dermat. u. Syph. **53**:269-312, 1900.

17. Warthin, A. S.: A Case of Endothelioma of the Lachrymal Gland (Myxo-Chondro-Endothelioma Cylindromatodes), with an Analysis of Previously Reported Cases of Lachrymal Gland Tumors, Arch. Ophth. **30**:601-620, 1901.

18. Colmers, F.: Ueber Sarkome und Endotheliome des Penis; im Anschluss an die Beobachtung eines Blutgefässendothelioms der Corpora cavernosa, Beitr. z. path. Anat. u. z. allg. Path. **34**:295-330, 1903.

19. Burkhardt, L.: Sarkome und Endotheliome nach ihrem pathologisch-anatomischen und klinischen Verhalten, Beitr. z. klin. Chir. **36**:1-122, 1902.

20. Lazarus-Barlow, W. S.: The Elements of Pathological Anatomy and Histology for Students, London, J. and A. Churchill, 1903.

elements are present. Coenen,[21] in 1905, described lesions on the scalp similar to those reported by Wolters. Wood,[22] in the same year, reported a case of endothelial tumor of the testicle with metastasis in the kidney, liver and lung. He believes that endotheliomas are directly related to sarcomas.

Lazarus-Barlow,[23] in 1906 and 1907, expressed the belief that the supposed phylogenetic origin of these tumors, combined with the method of arrangement of normal endothelium, should lead one to expect that endotheliomas would show great structural variation ranging between that presented by a typical spheroidal-cell carcinoma on the one hand to that of a typical sarcoma on the other. He contended that the group of endotheliomas in man must be enlarged to include certain growths of the breast, cervix and so forth, which heretofore had been considered carcinomas. He maintained, further, that the variations in certain growths in the human uterus and certain mouse tumors are explicable on the theory that such growths are endotheliomas.

Zeit,[24] in 1908, asserted that tumors which cannot, from a pure histogenic and morphologic point of view, be classified as either epithelial or connective tissue tumors should be called endothelial tumors. He explained their polymorphous structure on the supposition that the mesoderm comes from both the ectoderm and entoderm. Tumors of mesodermal origin, then, might have epithelial characteristics by reversion to their double embryonal anlages, or again might resemble connective tissue growths from mesoderm as such. Zeit described the clinical picture of endothelioma as differing from that of either carcinoma or sarcoma.

Ziegler,[2] in 1908, said that we should consider the endothelioma as a special form of sarcoma, and that endotheliomas in general often so closely resemble sarcomas that they cannot be distinguished from them. He says, "It is by no means determined that endothelial cells of lymph spaces and vessels do not take part in the formation of sarcomas." Delafield and Prudden,[3] in 1914, said that the stroma of an endothelioma may become sarcomatous. In 1908, 1909 and 1910,

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21. Coenen: Ueber Endotheliome, Deutsch. med. Wchnschr. **31**:1131-1132, 1905.

22. Wood, E. J.: Report of a Case of Metastatic Endothelioma, Am. J. M. Sc. **130**:642-643, 1905.

23. Lazarus-Barlow, W. S.: The Histological Diagnosis of Endotheliomata, Arch. Middlesex Hosp. **7**:79-87, 1906; Glasgow M. J. **68**:265-274, 1907; The Relations of Endothelioma to Other Forms of New Growth, Proc. Roy. Soc. Med., Path. Sect. **1**:167-172, 1908.

24. Zeit, F. R.: Morphologic and Histogenetic Characteristics of Endothelial Tumors, J. A. M. A. **46**:567-576, 1906.

respectively, Hansemann,[25] Minne,[26] and Lofaro[27] described tumors of endothelial origin occurring in the skin. These tumors presented malignant characteristics, and the histology was that of endothelioma. Börst,[28] in 1913, reported similar tumors of the pleura, peritoneum, dura and skin, and designated those occurring in the pleura and peritoneum as mesotheliomas.

A gradual change in the trend of opinion and a decline in the opposition to the concept of endothelioma has occurred during the last five years. Matheny,[29] Fraser,[30] Schöppler,[31] Kron,[32] Pernet[33] and Kettle[34] reported cases of tumors, the structure of which characterized them as tumors of endothelial origin. Common features of all were the polymorphic-cell type of growth, the whorl arrangement of the cells, the formation of elongated cell strands and narrow trabeculae, and the formation of vacuoles which coalesce to form sinuses and channels which contain blood. These authors define endotheliomas as tumors of mesodermal origin, the cells of which tend to differentiate into flat endothelial cells such as form the intima of blood and lymph vessels, and the inner surface of certain cavities or spaces such as the pleura, peritoneum and the arachnoid and subdural lymph spaces. They are characterized as hemangio-endotheliomas if the tumors arise from cells lining blood vessels, and as lymphangio-endotheliomas if they arise from cells lining lymph or serous spaces. The tumors are also classified into perivascular, endovascular and peri-endovascular, depending on whether the original cells are in the perithelium, the endothelium or both.

ORIGIN OF THE TUMOR

A history of trauma was reported in thirteen (48 per cent.) of the cases. In general, the clinical course in cases reported in the

25. Hansemann, D.: Ueber "Endotheliome," Deutsch. med. Wchnschr. **22**: 52-53, 1896.

26. Minne: Endotheliomes endolymphatiques flexiformes primitifs et secondaires de la peau, J. med. de Bruxelles **14**:226-231, 1909.

27. Lofaro, P.; Endotheliom auf einem dermoidalen Mutternaevus, Deutsch. Ztschr. f. Chir. **106**:537-557, 1910.

28. Börst, M.: Quoted by Schöppler (Footnote 31).

29. Matheny, A. R., and Wallgren, A. B.: Report of Two Cases of Sarco-Endothelioma (Plexiform Angiosarcoma), Penn. M. J. **21**:143-145, 1917-1918.

30. Fraser, J.: The Hemangioma Group of Endotheliоblastomata, Brit. J. Surg. **7**:335-342, 1919-1920.

31. Schöppler, H.: Ueber ein Endotheliome sarcomatodes, Centralbl. f. allg. Path. u. path. Anat. **30**:323-329, 1919-1920.

32. Kren: Ein echtes Haemangioendotheliom, Wien. klin. Wchnschr. **30**:26, 1917.

33. Pernet, G.: Case of Multiple Infective Lymphangio-Endothelioma, Proc. Roy. Soc. Med., Dermat. Sect. **13**:17-21, 1920.

34. Kettle, E. H.: Tumours Arising from Endothelium, Proc. Roy. Soc. Med., Path. Sect. **11**:19-34, 1918.

literature, as in my own, is that of a tumor of slow growth, developing at the site of former trauma. The lesions do not produce metastasis until late, when the tumor has reached considerable size. The tumors in all reported cases exhibit a marked tendency to bleed. A similar tendency was evident in my cases. The late metastasis is in marked contrast to that in carcinoma. The results of early excision with thorough removal are good, and the outlook apparently is much better than following removal of either carcinoma or sarcoma.

TABULATION OF TWENTY-SEVEN REPORTED CASES

	Cases	Per Cent.
Sex		
Males	20	74.7
Females	5	18.5
Sex not given	2	7.4
Age		
1 to 5 years	1	3.7
21 to 30 years	3	11.1
31 to 40 years	5	18.5
41 to 50 years	11	40.7
51 to 60 years	4	14.8
Age not given	3	11.1
*Location of Initial Lesion**		
Lower extremities	6	22.2
Upper extremities	4	14.8
Skin (location not given)	4	14.8
Thorax (pleura)	3	11.1
Chest	1	3.7
Head	1	3.7
Bone	1	3.7
Lacrimal gland	1	3.7
Penis	1	3.7
Testicle	1	3.7
Scrotum	1	3.7
Location not given	2	7.4
Average Duration of Lesion		
Less than one year	1	3.7
1 to 2 years	4	14.8
3 to 4 years	1	3.7
4 to 5 years	4	14.8
5 to 6 years	2	7.4
6 to 7 years	1	3.7
7 to 8 years	3	11.1
8 to 10 years	2	7.4
10 to 13 years	2	7.4
13 to 14 years	1	3.7
15 years	1	3.6
Duration not given	5	18.5

* Metastasis occurred in twenty-four (89 per cent. of the cases.

Various opinions are offered in the literature with regard to the etiology of endothelial tumors. Frazer expressed the belief that they are congenital in origin, supposedly developing from "rests" in the early formation of the vascular system. This point, however, is quite as unsettled as in other cases of malignant tumors. The development of the tumor takes place by endothelial cell proliferation with the formation of embryonic blood vessels. Further development may vary in different ones. A tumor of this type may undergo arrest, or, while retaining its capillary characteristics, it may grow by infiltration into

and between the surrounding tissues; it may change from a capillary to a cavernous structure, or it may become compact and solid. In the latter, the endothelial cells form masses and whorls without capillary formation. This type probably is the malignant endothelial tumor which gives rise to metastasis.

Kettle has shown, by cutting entire nodules in serial section, that there is no physiologic connection between the blood spaces of the tumor and the vessels of the host. Small capillaries of the stroma rupture as a result of infiltration of their walls, and hemorrhage occurs into the surrounding tissues, forming cisterns, as it were, from which blood oozes into the vacuoles of the tumor. There is no true circulation of blood in the growth. As Kettle remarks, the condition is comparable to that in the early weeks of the development of the ovum where, as a result of rupture of the maternal capillaries, blood is extravasated into the choriodecidual spaces, and reaches the vacuolated spaces of the trophosphere. For this reason, hemorrhage is a common incident in the development of these tumors. The blood-containing spaces in the malignant endotheliomas merely represent an attempt on the part of the tumor cells to perform their normal function. The spaces result from a degenerative process which has its counterpart in the physiology of the normal angioblast, although it is quite uncontrolled in the malignant cell.

The degree of malignancy of endotheliomas, as in carcinoma and sarcoma, depends first, not on the morphology, histology or type of the original cell, but on the number and behavior of the individual cells. The higher the degree of differentiation, the lower the malignancy; the richer the tumor is in cells and the more independent of intercellular substance, the more malignant it is. The location of the lesion is important. The literature bears out the fact that, if the tumor is situated in a highly vascular area, or one rich in lymphatics, metastasis occurs more readily.

SUMMARY

1. Three cases are reported of tumors whose cellular elements present the histologic characteristics of endothelial cells.

2. The clinical course of the lesions in general is that of tumors of slow growth, often developing at sites of trauma. Metastasis does not appear until late, when the tumor has reached considerable size. The tumors in all cases exhibit a marked hemorrhagic tendency.

3. Clinically the lesions must be distinguished from syphilis, carcinoma, sarcoma, sporotrichosis and the infectious granulomas. The hemorrhagic character of the tumor, the relatively benign course of the lesion, the long delayed metastasis, and the good general condition

of the patient are features which should lead one to suspect malignant endothelial tumor. A final diagnosis, however, is practically impossible without histopathologic study.

4. Because of the variability in arrangement of endothelial cells, the ability of the cells to undergo metaplasia, the distortion of the original picture by secondary factors, such as infection, and the difficulty of tracing the tumor cells through their transition stages to preexisting endothelium, the earliest lesions obtainable should be employed in the histopathologic study.

5. The histologic structure of the tumors is that of an undifferentiated polymorphic-cell type of growth presenting a whorl arrangement of the cells with the formation of elongated strands and narrow trabeculae. There is definite evidence of an attempt to differentiate into vascular structures. A constant feature is the occurrence of vacuoles in the cytoplasm of practically all cells. These vacuoles coalesce with the resultant formation of large spaces. The cells bordering on these spaces arrange themselves in rows, become elongated, and form an endothelial lining of the space. There is a close association of the tumor with blood vessels. Capillary and sinus-like channels are formed which may contain blood, but have no apparent connection with the circulation of the host.

6. According to the interpretation which is placed on the morphology and histogenesis of the endothelial cell, the tumor may be regarded either as a structure of mesoblastic or connective tissue origin, histogenetically a sarcoma, or it may be regarded as a tumor composed of cells resembling epithelium, and hence, morphologically carcinoma.

7. The term endothelioma, as applied to my cases, represents a compromise between the histogenetic and the morphologic views of the classification of tumors.

8. Treatment consists of radical surgical removal of the original process followed by roentgen-ray or radium application to the site of the original lesion and to all probable areas of metastasis.

9 A gradual change in current opinion and a decline in the opposition to the conception of endothelioma as a type of neoplasm have occurred during the past five years. The three cases which I have described help to substantiate the belief that malignant endothelioma is an actual pathologic entity.

MELANOBLASTOMA OF THE NAIL-BED (MELANOTIC WHITLOW)

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HALSTEAD, KAN.

DEFINITION

Under this head may be described a malignant disease of the nail-bed marked by the formation of nodules of neoplastic tissue about the border and beneath the nails. The growth is characterized by the formation of melanin and a tendency to spread by way of the lymphatics. Hutchinson called this condition melanotic whitlow, a designation obviously inapt in the more advanced cases. I have adopted the term "melanoblastoma," in harmony with the teachings of Mallory, in order to emphasize the fact that, genetically, they are different both from the sarcomas and carcinomas.

INCIDENCE

The condition is rare, though obviously not so rare as the literature would indicate. The reported cases do not much exceed twenty. It has been my privilege to treat two of these patents, and, since American literature is all but devoid of case reports, a presentation of my cases, together with a general summary of the recorded cases, will be presented here. The case histories resemble each other so closely that a detailed account of each is uninteresting. Since, however, the literature is not readily accessible, the principal papers heretofore published will be presented in abstract.

REPORT OF AUTHOR'S CASES

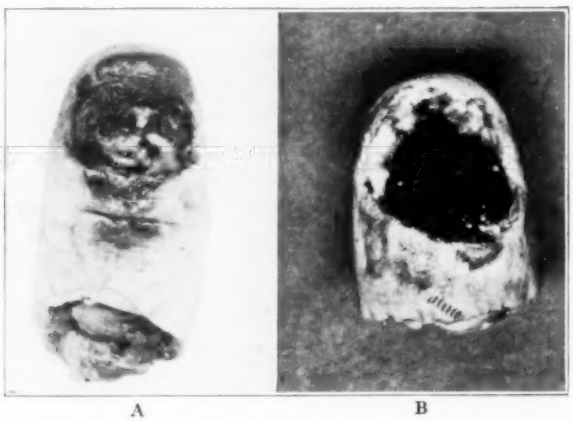
CASE 1.—A widow, aged 64, a year and a half previously, as a result of a slight injury, had an ulceration beginning along the outer border of the left thumb nail. It was treated with iodin and salves without result. In a year, the greater part of the nail-bed had become involved, and the nail was removed. The pain had never been severe, but it was a constant annoyance. The pain became severe after prolonged use of the thumb.

When she came under my care, the nail was absent and the nail-bed was occupied by a blue-black granular area (Fig. 1, *A*). To the touch, the nodules were firm and did not tend to bleed. About the border of the granular area was a border of darkly pigmented tissue. About the relatively unchanged skin small deeply colored areas could be seen through the epidermal covering. There was no involvement of the neighboring lymphatic glands.

The thumb was amputated. It is now two years since the amputation, and the patient still is free from evidence of recurrence.

CASE 2.—A woman, aged 54, four years previously, first noticed a black spot under the left thumb nail near its base. The spot was then about the size of a

black-headed pin, and looked like a blood blister following a bruise, but there had been no injury and it was not painful. About three months later, the center of the nail became white, dry and scaly and stripped off very easily. In a few months, this central strip of nail had completely separated itself, leaving a strip of healthy nail on either side with a hard, dry surface beneath. There was no soreness, but the area was sensitive to slight injury. The condition remained the same a year and a half. At this time, the remaining portions of the nail became dry and separated. The original black spot did not change until six months ago, when it began to spread and grew up like a wart. It now became sensitive. The patient attributed this to the innumerable slight injuries it received while she was nursing a sick daughter. She tried many kinds of salves and it was burned out a number of times by a physician. Following this the previously healthy skin at the base became brown. Five weeks previously, she had consulted another doctor. He sent her to a dermatologist who applied radium. The condition grew rapidly worse under this treatment and became excessively sensitive.



A B

Fig. 1.—*A*, the nail-bed is covered with dry granulations. The surrounding skin is well preserved. At the base of the nail-bed, the tumorous masses are approaching the skin surface from beneath. *B*, the nail-bed is covered with a granular mass in which hemorrhages have taken place. The surrounding skin is in part exfoliated, exposing the developing tumor masses beneath. Above the nail-bed, the tumor masses are still covered with unchanged skin, but they are well distinguished by their color.

When the patient came to see me the nail-bed had a granular surface covered with recently coagulated blood (Fig. 1, B). The granules appeared to have some hemorrhage into their substance. The whole surface was blue-black. The skin surrounding this area was hard, dry and yellowish white. Near the border of the lesion, small brownish black spots shimmered through. The lesion was very sensitive to the slightest touch. The lymph channels and lymph nodes were not involved.

An amputation at the midphalangeal joint was made. Healing took place without reaction.

This patient was operated on only two months ago, hence a recurrence for some time is not to be expected.

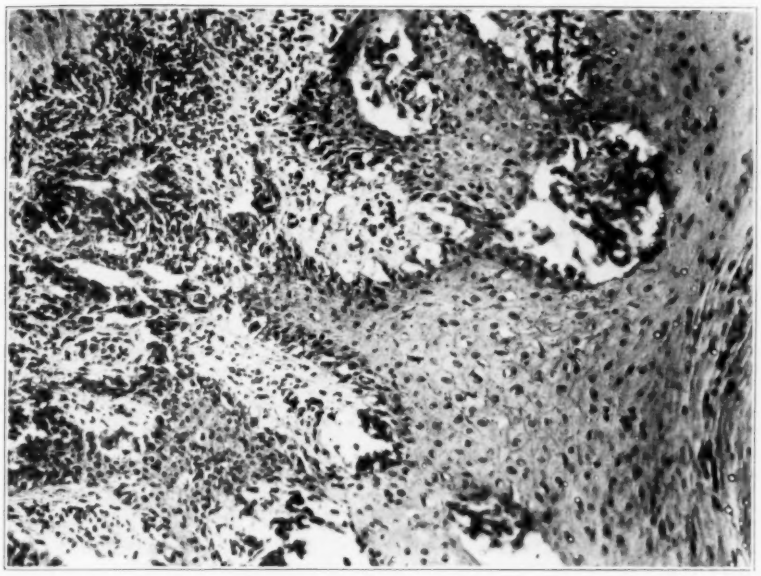


Fig. 2.—Slide from Case 1: The cell masses extend down from the papillary layer of the skin. The farther they advance the more elongated they become. Distributed among and within these cells are abundant pigment granules.

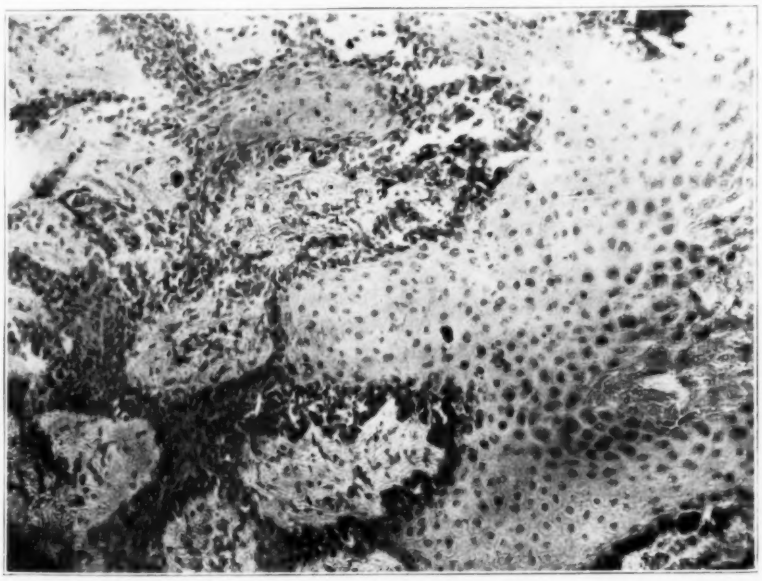


Fig. 3.—Slide from Case 2: The histologic findings are parallel with those in the preceding case.

Following are the only clearly typical cases that could be found in a somewhat extended search of the literature.

CASES IN THE LITERATURE

Case 3 (Boyer[1]).—A man, aged 57, presented a tumor the size of an egg on the little finger of his left hand. The tumor developed thirty years before as a little black line about the finger nail. This remained stationary for twenty-eight years. During the last two years, the line had become inflamed and extended in breadth and was painful. It became nodular as the size increased. The finger was amputated.

Case 4 (Demargnay and Monod[2]).—A woman, aged 59, had a tumor occupying the thumb of her left hand by covering the second and part of the first phalanx. It was dark and bled easily. It began as an excresence near the nail-bed. It had been removed some months previously and the base cauterized. It reappeared and hard masses appeared in the axilla, and an indurated cord could be felt along the arm. The slide showed large cells containing nuclei and nucleoli.

Case 5 (Annendale[3]).—The patient, aged 56, fifteen months before, had observed a small red ulcer, formed beside the nail of the right index finger. The nail was removed, but the lesion spread. A fungus mass formed, extending to the palmar surface. There was a fine line of demarcation between the denuded and the normal tissue. A strip of skin separated the dorsal from the palmar nodules. After amputation, the dorsal part was found to be pigmented, the palmar pigment free. The slide showed cells of all forms.

Case 6 (Nieberg[4]).—A man, aged 51, a year and a half before, suffered an injury to the ungual phalanx of his left thumb. A granular area appeared along the nail border, which was frequently cauterized and finally removed. This failing to cure, amputation was performed. Metastases in the axilla followed, these lesions containing pigmented cells. Necropsy showed extensions of the nodules along the vessels to the aorta and vena cava.

Case 7 (Willett[5]).—A woman, aged 80, had a more or less spherical growth springing from and surrounding the ungual phalanx of the thumb. The surface was nodular and uneven, the skin ulcerated. The nail still embedded in the growth was pushed upward from its bed. The lesion appeared strictly limited to last phalanx, which was involved so that the remains of the bone could not be made out. Amputation was performed. The growth consisted, microscopically, of irregular masses of deeply stained nucleated cells. The cells appeared to be epithelial, similar to those forming a healthy nail. They did not grow from the surface. Their arrangement recalled the structure of rodent ulcer. There were no cell nests. Three years later, there was a mass in the axilla.

Case 8 (Sacin and Keser[6]).—A man, aged 62, developed the lesion six years before entering the hospital, following a small lacerated wound. An ulcer was

1. Boyer: Gaz. méd. de Paris, 1854, p. 212.
2. Demargnay and Monod: Gaz. d. hôp., 1855, p. 415.
3. Annendale: The Malformations, Diseases and Injuries of the Fingers and Toes and Their Surgical Treatment, Edinburgh, 1865, p. 167.
4. Nieberg: Diss. Würzburg, 1882, p. 27.
5. Willett: Tr. Path. Soc., London **46**:152, 1895.
6. Sacin and Keser: Jahresb. ü. d. chir. Abt. d. Spit. in Basel, 1885, p. 114.

formed which secreted abundantly, covering the second and third phalanges of the fourth finger, elongated, with an irregular surface showing pigmented areas. The cervical and axillary glands were enlarged. Amputation was performed. The end-results are not stated.

Case 9 (Hallé[7]).—A man, aged 46, presented an affection of the thumb which had existed seven years. The nail became deformed, shriveled up and cracked, and finally came off completely. The area of the nail became red and thickened. An incision was made into it, but only blood escaped. The wound did not heal, and the tumor advanced. Curettage and cauterization with a hot iron was performed, followed by a recurrence. A granular surface, dark red, with some dark spots sharply defined from the surrounding pale skin, developed. Amputation of the thumb was performed and two glands were removed between the biceps and the brachial artery.

The tumor was firm and black on section and sharply limited. The skin was destroyed over the surface. The glands removed from the arm were ovoid and definitely encapsulated. The section showed pigment. The slide showed large fusicellular alveolar sarcoma, more or less pigmented.

Case 10 (Hutchinson[8]).—A man, middle-aged, presented a thickened nail along one edge of which was a black line which looked as if it had been touched with lunar caustic. Amputation was performed. Eight or ten years later, the disease recurred, involving the axillary glands.

Case 11 (Hutchinson[9]).—A middle-aged man presented a tumor which had been growing on his thumb for several years. The growth was as large as a walnut. It was ulcerated over the whole surface, but showed no tendency to slough or become fetid. Just under the overhanging border of the unswollen skin was a narrow coal black margin.

Case 12 (Lediard[10]).—A woman, aged 40, had a small melanotic tumor growing from the side of the nail of the index finger. The growth was painless for two years. The nail was torn off, the growth clipped off and the phalanx scraped. The finger was amputated two days later, after examination of the tumor had been made. The growth was three quarters of an inch (1.8 cm.) long, one-half inch (1.2 cm.) broad and three quarters of an inch deep. The patient died two years later of numerous melanotic tumors, distributed over the body.

Case 13 (Faguet[11]).—A woman, aged 63, two years before, ran a splinter under the medial border of the left ring finger. The splinter was not removed and a phlegmonous inflammation developed. The splinter was finally expelled, but left a fistulous tract and a tumefied area. Later, a black nodule the size of the head of a pin developed near the fistulous opening. This spread, finally covering the entire nail-bed.

When examined by the author, the entire phalanx had been completely destroyed. The surface of the extremity of the finger was covered with a black, granular, ulcerating surface. The consistency was hard, particularly at the base. Three or four glands the size of a little nut were discovered in the axilla.

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7. Hallé: Bull. de la Soc. Anat. de Paris **58**:436, 1883.
8. Hutchinson: Am. J. M. Sc. **91**:470, 1886.
9. Hutchinson: Tr. Path. Soc., London **36**:468, 1885.
10. Lediard: Tr. Path. Soc., London **39**:307, 1888.
11. Faguet: Arch. clin. de Bordeaux, 1894, No. 18, p. 448.

At operation, seven glands, black on section, were found in the axilla. Metacarpophalangal amputation of the finger was performed. The section of the tumor was mottled black and brown, with lighter areas. The slide showed small round cells, separated from one another by small bundles of connective tissue. Other areas show definite epithelial structure, without intercellular connective tissue, but with elongated cells.

Case 14 (Coley, W. B.[12]).—A man, aged 37, seven years before observation, had bruised his thumb. Several years later, he bruised it again. It soon became painful, and five months later discoloration about the nail appeared. It was examined by L. L. McArthur, who called the lesion melanotic sarcoma of the round cell type. Amputation was performed, and a few months later shot-like nodules appeared in the skin of the wrist. Soon similar tumors occurred in various parts of the body. The patient was treated with toxins, and improvement followed, but soon large tumors appeared, and the patient died.

Case 15 (Trimble, Wm. B.[13]).—A woman, aged 39, two months before had run a splinter under the thumb nail. Suppuration followed, and a growth the size of a walnut developed. The palmar surface of the skin remained unaffected. The tumor was a fungus mass which overlapped the healthy skin. Amputation was performed.

Case 16 (Trimble, Wm. B.[13]).—A man, aged 45, whose nail, six months before observation, split slightly, and later came off entirely, noticed small pigmented spots in the nail bed. When first examined, the thumb showed a large fungus mass 2 by 3 inches (5 by 7.5 cm.) involving the whole distal phalanx. Amputation was performed.

Specific treatment was given in each case for a month, without result.

Case 17 (Murphy, J. B.[14]).—A man, aged 56, six years before, noticed a slight serous discharge with reddening and irritation under the tip of the nail of the right middle finger. The finger was amputated three years later.

Five weeks later, enlarged epitrochlear and axillary nodes were removed. Two years after this, a node the size of a coconut appeared in the axilla. This was removed.

Murphy assumed that the tumor arose from the irritation of a "wart."

PATHOLOGY

Both of my cases represented a relatively early stage of the disease. They both presented the characteristic black border about the lesion. The lesion was granulomatous and looked out through a relatively unchanged skin. In some situations, small black points could be seen shimmering through the skin. This is well shown just about the nail-bed in Figure 1. The important point in the gross appearance is the fact that the growth seems independent of the skin, growing from beneath and displacing it.

The slides from my cases resemble each other so closely that the same description applies to both. Just beneath the epithelial layer, the

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12. Reported in discussing a paper by Galloway on pathologic pigmentation preceding malignancies.

13. Trimble: Am. Med. **5**:788, 1903.

14. Murphy: Murphy's Clinics **14**:663, 1915.

tumor cells extend in more or less fringelike arrangement (Figs. 2 and 3). These projections seem to be direct continuations of the epithelial layer. The projections extend downward with little tendency to nest formation. The cells tend to become elongated and the nuclei pronouncedly ovoid. The continuation from the epithelial cells is only apparent. Because of the subsequent development and the clinical course, we are warranted in assuming that it is the chromatophore cells that form the starting point of these tumors.

PATHOGENESIS

The genesis of pigmented tumors has been much discussed. Ribbert is of the opinion that they are derived from the chromatophores. These cells lie beneath the epidermis, particularly along the blood vessels. Gibson and I [15] made a study of the pigmented tumors of the lower extremity. We showed that the clinical course of all pigmented tumors was strikingly similar, though the histologic structure may vary markedly. In Figure 16 of our paper, the histologic picture resembles the slides from the cases herein reported. Other slides, as Figures 15 and 17, show, respectively, an alveolar and a spindle form arrangement. We pointed out that, notwithstanding the variation in the histologic appearance of the physical characters of the tumor on the slides, the clinical course is the same. The tendency is to local recurrence, particularly spreading to the neighboring lymph glands or along the lymphatics.

Exactly the same thing is observed in the tumors of the nail-bed of the fingers. Local recurrence and lymph gland metastases are reported in all cases in which the course has been followed long enough. The histologic diagnosis of the reported cases has shown a great variation, carcinoma, sarcoma and sarcocarcinoma. In all these pictures, the clinical course is the same. It seems fair to assume that when the course is so markedly similar, the underlying conditions must be the same.

The clinical course and the histologic picture resemble the like lesion of the lower extremity. I believe the term "melanotic whitlow" should give place to the more accurate term "melanoblastomas of the nail-bed."

DIAGNOSIS

The appearance of a slowly developing granular area about the nail-bed, showing a pigmented border is characteristic of the disease. When the nail has been lost at the time that the examination is made, the history of onset and the deep pigmented areas beneath the otherwise unchanged skin leave no doubt as to the nature of the disease.

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15. Hertzler and Gibson: Ann. Surg., July, 1914, p. 89.

PROGNOSIS AND TREATMENT

Apparently, all patients so afflicted sooner or later die of the disease. Some have remained free as long as ten years.

From what we know of like lesions in the lower extremities, there is reason to hope that early diagnosis and prompt amputation may produce a cure. Roentgen ray and radium, in these as in all melanotic disease, are worse than useless.[16]

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16. In addition to the references already given, the following will be found of interest:

Galloway: Brit. M. J. **2**:873, 1897.

Wheeler: Proc. Path. Soc., Dublin, 1880-1881, N. S. 9, p. 171.

THE KOLMER MODIFICATION OF THE WASSERMANN REACTION

A REPORT OF ITS TRIAL IN A SERIES OF ONE THOUSAND AND FOURTEEN SERUMS *

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There are few laboratory procedures in common use which have aroused greater interest in the recent past or have been subjected to more intensive and extensive investigation than the complement-fixation reaction as applied to the serologic diagnosis of syphilis, or, as it is commonly known, the Wassermann reaction.

Both investigation and discussion have centered on two points: its reliability and the exact significance to be placed on the results obtained, and matters of technic as affecting the delicacy and reliability of the test. It is to be regretted that these two important phases of the question have not infrequently been discussed and investigated as separate entities rather than as intimately related factors of a most complicated and intricate problem.

It is impossible artificially to assign to this reaction a predominant value in any set stage of syphilis. If an arbitrary division is to be made, it seems fair to conclude that its value as a means of diagnosis can hardly be overestimated, as it is on the early diagnosis and the prompt initiation of treatment that the greatest hopes of ultimate success are firmly founded; on the other hand, without a reliable criterion by which to determine when treatment can be discontinued with any degree of safety, the management of syphilis and the avoidance of late and often intractable complications, while a "consummation devoutly to be wished," presents a problem of the utmost difficulty.

It is true, of course, that absolute dependence as to the absence of syphilitic infection, or an exact degree of safety and confidence as to a sufficiency of treatment cannot—and should not—be determined by the results of a single Wassermann test, and this fact is well known and admitted. Nevertheless, in the present state of our knowledge, it can be safely said that the Wassermann reaction constitutes the most constant single symptom of the disease, even though at times too great a reliance has been placed on the findings of a single examination.

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* From the Laboratories of the Pittsburgh Hospital.

While much has been added to our knowledge concerning the reaction, much still remains to be elucidated. In spite of prolonged and extensive investigations by various workers, the true nature and mechanism of the production of the substance producing the reaction is still unknown.

Many factors concerned with the proper conduct and interpretation of the test have been brought to light, however, and on one phase of the question both serologist and clinician are in thorough accord: the vital necessity for the development of a standard technic which, exclusive of its value per se, will permit of a comparative analysis of the results of the test as conducted by workers of every community, which will form a reliable basis for diagnosis and an equally reliable criterion of the effects of treatment. The importance of this need has long been recognized and often proclaimed and the efforts of many investigators, therefore, have been directed toward this end with the resultant proposal of several "standard" methods.

The solution of the problem presents many difficulties arising both from the inherent complexities of the subject per se and as a natural concomitant to the personal preferences of individual workers, each of whom, using a method satisfactory to himself and tried in the fires of his experience, is naturally reluctant to abandon or modify it in favor of another. As a result, most of the proposed "standard" methods represent the personal preference of individuals fortified by prolonged experience.

It becomes obvious, therefore, that the evolution of any method having a legitimate claim to be adopted as a standard must follow directly on a careful, keen, unbiased and minute analysis of every possible phase and factor entering into the reaction. The technic must arise from and be based on the results of such studies and must present a logical basis for the modifications it involves, and must be subjected to fair, impartial and extensive investigation to determine whether or not the results indicated by the premises on which it is founded can be substantiated in the light of practical experience.

Such a study has recently been concluded by Kolmer and his associates, as a result of which Kolmer [1] has presented for trial a technic based on a careful study and analysis of the results of their work.

Through the courtesy of Dr. Kolmer the details of this proposed new method were made available to these laboratories some time in

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1. Kolmer, J. A., and Associates: Studies in the Standardization of the Wassermann Reaction, a series of thirty-two papers published in the Am. J. Syph., 1919-1921. Kolmer, J. A.: New Complement-Fixation Test for Syphilis Based on the Results of Studies in the Standardization of Technic, Am. J. Syphilis **6**:82 (June) 1922.

advance of their publication, and I shall present the results of a trial of the method in a series of 1,014 cases tested by parallel methods.

Any technic offering itself as a standard method to supercede and push aside all others must, of necessity, be subjected to careful, extensive and analytic study before its unquestioning acceptance can be advocated; the results of this comparatively small series are of interest only as indicating, to some extent, the degree of usefulness of the method under ordinary routine conditions, and as acting as a possible stimulus to its comparative trial and the resultant accumulation of more voluminous statistics by others.

As has been noted in the foregoing, if the importance of the Wassermann reaction in the management of syphilis can be arbitrarily subjected to gradation, there is some justice for the contention that it is at least of great importance as affecting the matter of diagnosis. So far-reaching are the consequences, to the patient, his family and his associates, of either a false positive or a missed diagnosis, and so great has oftentimes been the unwarranted confidence placed in the results of isolated tests that the development of a technic the results of which may be looked on with a high degree of confidence is a matter the importance of which cannot be overestimated. Of no less importance is it that the method should prove equally delicate and reliable as a criterion for the estimation of the efficiency of treatment.

So far as can be at present ascertained, certain generalities seem justified: (1) In the present state of our knowledge concerning the complement-fixation reaction it does not seem likely that this method of examination presents a possibility of infallible diagnosis, nor that it—or any other method—because of factors inherent in the disease itself, can be depended on to detect unerringly the presence of syphilitic reagin at any and all stages of the disease. (2) The substance or substances now, for want of definite knowledge, grouped under the term "reagin," are not produced in constant mathematical proportion in various stages of the disease. (3) Because of these two facts, absolute reliance must not be placed on the results of a single Wassermann reaction, which should not be made the basis for dogmatic diagnostic or prognostic assertions. (4) No matter what the technic the results of the test must always be approximated with and interpreted in terms of all the other findings in the case at hand.

The problem as it presented itself in the investigation herewith reported was, therefore, to determine, as far as possible, the degree of delicacy to be imputed to the technic on trial and the degree to which reliance could be placed on the findings obtained with it, without any attempt to discuss the premises on which the modification is based, as these have been amply and thoroughly covered in the investigations of which this modification is the sequel.

Owing to the inability of the laboratory to regulate the type and character of the case tested, it was not possible to collect a large number of any one kind; indeed, this was not attempted as it was felt that greater interest might arise from a consideration of the results of the examination of unselected serums. The serums tested, therefore, were examined just as they came from the following sources:

1. Specimens taken as a routine in the wards of the Pittsburgh Hospital, the majority being taken for informative purposes with or without a possibility of syphilitic infection.

2. Specimens sent to the laboratory for diagnosis or as a control of syphilitic treatment.

3. Specimens from "Morals Court" cases forwarded by Dr. A. H. Eggers, to whom acknowledgement is due for his aid in securing "follow-up" data concerning them.

These last cases comprised those of many known prostitutes, the determination of whose infectivity was a matter of great interest, those of many known syphilitic persons, and many cases at various stages of treatment.

Ordinarily the Wassermann reaction is made in these laboratories on every day but Monday, Thursday and Sunday. The Kolmer method was performed on Tuesday and Friday.

While the majority of the serums were tested within twenty-four hours of their reception, many, such as those received on Tuesday afternoons, for example, were held over until the following Friday so that the Kolmer method might be used. Hospital specimens, as a rule, were examined within twelve to twenty-four hours of their collection. "Outside" specimens and those from Dr. Eggers were sometimes not received until from twenty-four to forty-eight hours after collection; they were occasionally hemolyzed in varying degree, and were subsequently, of necessity, held in the laboratory for a further period before being tested by the Kolmer method.

This was not looked on as a disadvantage but rather as approximating the conditions obtaining in laboratories in general, especially those receiving specimens from a wide area, and represents the conditions confronting any method proposed for standard or general adoption.

All serums of this series were tested by two technics; one, the routine method used in this laboratory, hereafter referred to as "routine"; the other, the Kolmer method, hereafter called "Kolmer."

In all instances complement, sheep cells, amboceptor, salt solution and inactivation period were identical in both methods.

All serums were separated from the clot as soon as received, except hospital serums, which were allowed to stand for some hours, placed in sterile, stoppered tubes, and kept at a temperature of from 4 to 6 C. until examined by both methods.

On Tuesdays and Fridays both tests were made, one immediately after the other; on the intervening days the routine method was performed, the Kolmer test of the same serums being made on the subsequent Tuesday or Friday as the case might be.

TECHNIC OF ROUTINE METHOD

Serums: These were inactivated for fifteen minutes at 56 C. and used in doses of 0.1 c.c. No attempt was made to test for or remove the natural antisheep hemolysin.

Salt Solution: An 0.85 per cent. solution was freshly prepared by diluting a stock 8.5 per cent. solution of dried chemically pure sodium chlorid 1:10 with sterile distilled water.

Complement: Preserved complement was used throughout in order to permit the use of the same complement in both methods. The pooled serum of four guinea-pigs was preserved both by the Rhamy method (the addition of one and one-half parts of 10 per cent. sodium acetate in physiologic sodium chlorid solution to each cubic centimeter), or by the addition of 0.3 gm. of dried sodium chlorid to each cubic centimeter of serum as advised by Kolmer. The treated complement was then kept frozen.

The former method of preservation was used in approximately three-fourths of the series, and the latter in the remainder.

Complement titration in 1:10 dilution was performed immediately before the main test, using a constant dose of 0.1 c.c. of amboceptor and 0.5 c.c. of a 2.5 per cent. suspension of sheep cells with water-bath incubation for one hour at 38 C. At the end of this time the unit of complement was read as the smallest amount giving complete hemolysis and twice this amount, or two units, used in the main test.

Amboceptor: Antisheep amboceptor was preserved by the addition of equal parts of chemically pure glycerin in ampule of 1 c.c. amounts, each ampule, therefore, containing 0.5 c.c. of serum. The contents of one ampule were transferred to a sterile, glass-stoppered bottle and diluted according to titer with sterile 0.85 per cent. salt solution so that 0.1 c.c. gave satisfactory hemolysis with a complement dose of 0.5 c.c. of 1:10 dilution, approximately 2 per cent. of 5 per cent. phenol in physiologic sodium chlorid solution added to prevent contamination, and the stock bottle was used until the supply was exhausted. The amboceptor throughout the series came from the same lot.

Sheep Cells: These were secured by bleeding the sheep (four animals bled in rotation to avoid producing undue fragility of the corpuscles) the day previous to the test in 10 per cent. sodium citrate in physiologic sodium chlorid solution; the cells were then washed four times the same day in physiologic sodium chlorid solution and twice more on the morning of the test, the supernatant fluid crystal being clear, as a

rule, in the last three washings. The final mass of washed cells was made up in 2.5 per cent. suspension in physiologic sodium chlorid solution.

Glassware: This was utilized for Wassermann purposes only and sterilized by dry heat for one hour at 160 C. All solutions, suspensions, etc., were made in sterilized tubes or flasks.

Antigens: A triple battery was used, consisting of the following:

1. Cholesterinized extract of human heart: an alcoholic extract of human heart muscle containing 0.4 per cent. cholesterin and used diluted 1:20 with 0.85 per cent. salt solution.

2. Acetone-insoluble lipoids of the human heart, diluted 1:10 with 0.85 per cent. salt solution.

3. Alcoholic extract of syphilitic (fetal) liver, diluted 1:10 with 0.85 per cent. salt solution.

All dilutions were freshly made as needed. All antigens were retitrated at monthly intervals and used in doses of not less than five times the antigenic unit, which amount was always from ten to twenty times less than the anticomplementary unit. The hemolytic unit was determined at the time of the original titration but not thereafter, and no extract was used until it had been run with tried antigens in not less than fifty to 100 tests to determine the constancy with which it reacted.

The Test: Four tubes were used for each serum, the first three for the various antigens, the last being the serum control. During the incubation of the complement titration, which was first set up, the test racks were prepared, serums numbered, requisitions and laboratory numbers checked, etc., and the antigen dilutions prepared. The antigen was then placed in the tubes, followed by the serum dose. An interval of from fifteen to twenty minutes then generally occurred before the complement titration could be read. The proper dose of 1:10 complement was then added, and the racks incubated for one hour at from 2 to 5 C. in an ice-water bath, according to the method of Duke.[2]

After the primary incubation period the racks were placed in the 38 C. bath for a few minutes (not more than five), and the hemolytic system added. Secondary incubation was at 38 C. in the water-bath, readings being made when the antigen and serum controls were hemolyzed.

Controls:

1. Corpuscle and salt solution control: 0.5 c.c. of cell suspension plus 2 c.c. salt solution; no hemolysis.

2. Amboceptor Control: Amboceptor dose plus dose of cells plus 2 c.c. salt solution; no hemolysis.

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2. Duke, W. W.: Ice Water-Bath in Complement Fixation for the Wassermann Reaction—a Shortened Technic, J. Lab. & Clin. Med. **6**:392 (April) 1921.

3. Complement Control: Dose of complement plus cell suspension plus 2 c.c. of salt solution; no hemolysis.

4. Antigen Control: Dose of complement plus dose of antigen plus salt solution plus hemolytic system after primary incubation; complete hemolysis.

5. Serum Control: One-tenth c.c. of serum tested plus dose of complement plus salt solution plus hemolytic system after primary incubation; complete hemolysis.

6. Positive Control: One-tenth c.c. of a mixture of several known positive serums; no hemolysis.

7. Negative Control: One-tenth c.c. of a mixture of several known negative serums; complete hemolysis.

Readings: These were made separately for each antigen on a $++++$, $+++$, $++$, $+$ basis.

The degree of fixation given by each antigen was noted separately, all three forming the complete report.

In accordance with observations recorded elsewhere,[3] a serum was considered positive if reacting to the cholesterinized antigen in $+2$ degree, even if the other antigens were negative.

The technic outlined in the foregoing, with the exception of the primary incubation in the ice-water bath, represents that which I used over a period of years and on the basis of results obtained and an analysis of records, is believed to be reasonably delicate and satisfactory, so much so as to form an acceptable balance by which to weigh the results obtained with the Kolmer modification and to present a fairly strict standard for comparison.

TECHNIC OF THE KOLMER MODIFICATION

The technic used was exactly as outlined in the original paper except that, in the last several hundred tests, the serum dilutions were rendered less abrupt from Tube 2 onward.

The serum dilutions as originally devised were as follows: 0.1, 0.02, 0.004, 0.002, and 0.001 c.c. With this range a large number of 44000 results (classed as moderately positive) were obtained, and it became obvious that the drop from 0.02 to 0.004 c.c. was too abrupt. A similar conclusion was reached and recorded by Kolmer,[4] and a change to the following dilutions advocated: 0.1, 0.05, 0.25, 0.005, and 0.0025 c.c. Following this change in the range of dilutions an increase in the flexibility of the readings was noted, and this series of serum dilutions appears to be in every way satisfactory.

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3. Kilduffe, R. A.: Concerning the Specificity of Cholesterinized Antigens in the Serologic Diagnosis of Syphilis, Arch. Dermat. & Syph. **3**:598 (May) 1921.

4. Kolmer, J. A.: Quantitative Fixation Test in Syphilis, Am. J. Syphilis, to be published.

Before proceeding to an analysis of the results obtained in the series it seems timely here to take note of some general factors concerned with the test as weighing for or against its permanent adoption.

It is not a technic to be readily acquired or grasped by the tyro—but then the tyro should not be permitted to sit in judgment on any question so gravid with important and far-reaching sequelae as the serologic diagnosis of syphilis or the serologic determination, so far as it can be determined, of the efficiency of treatment and the wisdom of the dismissal of a patient from observation.

To the experienced serologist, well grounded and at home in the intricacies of the subject, it presents absolutely no difficulty, and especially since the adoption of the new range of serum dilutions, the large series of tubes required for any considerable number of tests can be set up and filled with remarkable rapidity and certainty. By the accustomed eye no difficulty will be experienced in reading the results with a marked degree of accuracy; until experience is acquired, or in case of doubt, there is always a most ingenious and accurate reading scale for comparison.

From the standpoint of technical difficulty the new technic presents none that is insurmountable or even difficult to overcome, and extreme facility in its performance is rapidly and easily acquired.

The disadvantage of the added time necessitated before a report can be made, owing to the long incubation period, is more than counterbalanced by the greater delicacy of the test, as will hereafter be discussed; and the factors of expense, time and trouble in the preparation of the reagents and the conduct of the test can be disregarded.

The use of preserved complement decidedly lessens the expense of this item, and the new antigen used in the method [5] is so far in advance of any with which I am familiar as to render the expense of its preparation negligible. Indeed, the use of dried heart muscle powder which can be kept indefinitely, and the marked stability of the extract, together with the fact that it is very slightly anticomplementary and antigenic in dilutions as high as 1 : 2400, make it probably even a smaller item of expense than the continued maintenance of a supply of various extracts, which may require the preparation of several extracts before one which is entirely satisfactory is found.

If this new method had resulted in nothing more than this new antigen, a decided advance in technic would have been made.

Even at the expense of forestalling the analysis of the results obtained, some mention must be made of the clarity, distinctness and definite character of the readings. One is at once impressed with the

5. Kolmer, J. A.: A Superior Antigen for Complement Fixation Tests in Syphilis (a Cholesterinized and Lecithinized Alcoholic Extract of Heart Muscle), Am. J. Syphilis **6**:74 (June) 1922.

graphic and definite character of the results and soon acquires a sense of elation in the flexibility of the readings and the distinct separation into degrees of positiveness; where, before, between two plus four serums there is not a pin to choose, now there are definite, distinct and clearly outlined differences in the strength of the reaction graphically illustrating the intensity of the reaction to infection or a hitherto indistinguishable effect of treatment.

This feature alone constitutes no slight advance and advantage in the interpretation of the serologic index to the response to infection or the effect of treatment.

The readings are made on the basis of the degree of reaction in each serum dilution using a $++++$, $+++$, $++$, $+$, 0 scale; the reaction is, therefore, a strictly quantitative test, which, it is admitted, forms the sine qua non of any method satisfactory for general adoption.

The readings are recorded as follows: Each figure represents the degree of fixation obtained with the respective serum dilution. When familiarity with the technic is obtained, by the clinician as well as the serologist, the reaction can easily be grasped by the fixation figures—to call them such for convenience—which may be set down much like the figures for a colloidal gold test.

Very Strongly Positive: Fixation *in any degree* in the first four or all five tubes, that is, with 0.005 c.c. of serum or less, for example, 44310, 44441, 34210.

Strongly Positive: Fixation in any degree in the first three tubes or in 0.025 c.c. of serum, for example, 44000, 34400, 41100.

Moderately Positive: Fixation in any degree in the first two tubes or in 0.05 c.c. of serum, for example, 44000, 34000, 13000.

Weakly Positive: Fixation in any degree in the first tube only or in 0.1 c.c. of serum, for example, 40000, 30000, 10000.

Negative: No fixation in any tube of the series, for example, 00000.

As noted by Kolmer in his original communication and confirmed in this series, occasionally there will be, with a positive serum, a lesser degree of fixation in the first tube containing 0.1 c.c. of serum than in the other tubes containing lesser amounts of serum, as, for example, 34100.

The natural inclination is to ascribe this phenomenon to the presence of antisheep amboceptors naturally present in the serum, but this supposition is untenable, as the phenomenon occurs with hemolysin-free serum. It is possible that there are other serum constituents which interfere with the union of antigen and syphilitic reagin, or that, in some way yet to be explained, the phenomenon is analogous to that seen in the proagglutinoid zone of macroscopic agglutination tests. This occurrence, however, is infrequent, and presents no difficulty in making the readings as the strength of the reaction is gaged by the

smallest quantity of serum capable of giving fixation. As pointed out by Kolmer, it presents, however, an important possible source of error in technics in which doses of 0.1 or 0.2 c.c. of serum only are used.

Tables 1 and 2 give the gross results of the series with both methods. It will be noted that, first of all, there were fewer anticomplementary results with the Kolmer modification and that a larger number of positive results were obtained. Expressed in percentage, 1.5 per cent. more positives were obtained by the Kolmer modification than by the routine method.

AUTHOR'S SERIES

TABLE 1.—GENERAL RESULTS WITH ROUTINE METHOD IN AUTHOR'S EXPERIMENTS

Plus 4, all antigens	150
Cholesterin plus	93
Total plus, 243 or 2.39 per cent.	
Anticomplementary	36
Negative	735
Total number of cases examined	1,014

TABLE 2.—GENERAL RESULTS WITH KOLMER STANDARD TECHNIC IN AUTHOR'S EXPERIMENTS

Very strongly positive	82
Strongly positive	37
Moderately positive *	126
Weakly positive	68
Total positive, 313 or 3.8 per cent.	
Anticomplementary	22
Negative	679
Total number of cases examined	1,014

* The large number of moderately positive cases is in part accounted for by the fact that in the serum doses originally used the dilution between Tubes 2 and 3 was too abrupt; after the change in dilution, the number of moderately positive results was decreased in favor of an increase in the number of strongly and very strongly positive cases.

TABLE 3.—RESULTS WITH SERUMS ANTICOMPLEMENTARY BY THE ROUTINE TECHNIC

Anticomplementary by both methods	3
Negative with Kolmer technic	26
Positive by Kolmer technic	7
	36

Granting the validity of the additional positive reactions, the apparent gain in delicacy is not overwhelming, and were the analysis of the results to stop here, an entirely false idea would be obtained of the delicacy, reliability and flexibility of the new technic, factors only evident on a closer and more detailed scrutiny.

In Table 3 the results with serums anticomplementary to the routine method are grouped. Despite the fact that many of the serums were tested by the Kolmer modification when older than when tested by the routine method, a decided decrease in the number of anti-

complementary reactions is noted, and in a large proportion of the serums definite positive and negative readings could be made by the Kolmer method.

This is a factor of importance and value as obviating in many instances the necessity for the collection of a second specimen, often a matter of grave inconvenience and annoyance to both patient and clinician.

In Table 4 several points of decided interest are at once evident.

By the routine method of sixty-six such cases, forty-three or 65 per cent. were negative and twenty-three or 34 per cent. were positive

TABLE 4.—SERUMS FROM PATIENTS WITH SYPHILIS UNDER TREATMENT

Number	Routine	Kolmer	Number	Routine	Kolmer
3142	0	44000	617	0	00000
3264	0	44000	619	C 4	44400
3294	Plus 4	44440	109	0	00000
3425	C 4 A 4	44000	5173	0	44100
3482	0	40000	5235	0	44400
3769	C 4	44000	5347	0	40000
3883	C 4	44400	5481	0	40000
4192	0	44440	511	0	40000
4236	0	44440	6076	0	44100
4371	0	44440	536	0	10000
4709	0	44000	6584	0	44000
4862	0	44400	6076	0	44100
4885	0	00000	6786	0	4400
McK. 454	0	00000	6841	0	40000
McK. 458	0	44400	7309	0	44400
McK. 462	0	44000	7383	0	44440
McK. 480	Plus 4	00000	7407	0	44310
McK. 498	0	44000	607	0	44441
5590	0	44000	7533	0	44400
5684	0	44000	609	0	4441
5823	0	44000	173	0	10000
5917	Plus 4	44440	5639	Plus 4	00000
McK. 532	0	44400	513	C 4	00000
McK. 539	0	44000	7261	Plus 4	40000
6289	0	00000	3424	C 4	00000
6350	Plus 4	44400	4500	C 4	00000
6820	0	00000	4809	C 4	44000
6948	C 4 A 4	44000	4802	C 4	44100
7213	0	40000	5007	C 4	44000
7379	Plus 4	44440	513	C 4	00000
7380	0	40000	6348	C 4	Ae
7384	0	00000	7562	C 4	00000
7403	Plus 4	44440	7450	C 4	00000

in varying degree, many being cholesterin positive only. By the Kolmer modification, however, fifty or 70 per cent. were positive in varying degree, fifteen or 23 per cent. negative, and one anticomplementary.

In the positive cases the graphic character of the readings forming a definite index to the degree to which response had been elicited by the treatment, and presenting a possible basis for the estimation of the degree to which it should be further pursued, is obvious.

It is to be noted that of the known cases of syphilis, two (480 and 5639) plus four to all antigens with the routine method, were negative to the Kolmer modification; and six (7450, 7562, 513, 4500, 3420, and 513) cholesterin-plus by the routine method, were also negative to the Kolmer modification.

Disregarding, for the moment, any question as to the validity of the cholesterin-plus reactions, this gives a total of eight cases of known syphilis in which, by the Kolmer modification, negative reactions were obtained which probably did not represent the absence of syphilitic reagin.

This is in accordance with the known fact that syphilitic reagin may, at times, present a selective action in regard to antigens and is illustrative of the fallacy of relying on a single negative Wassermann reaction as a criterion for dogmatic assertions. Bearing in mind the work of Thaysen,[6] who demonstrated, in known syphilitic persons, a wide range of varying reactions from plus to minus or dubious occurring without explanation, with fluctuations in the same case from time to time, it is another illustration of the necessity for repeated observations and emphasizes the fact that the reacting substance in syphilis is not pro-

TABLE 5.—Diseases Other Than Syphilis

Disease	Routine	Kolmer
Pneumonia	Plus 4*	00000
Pneumonia	0	00000
Pneumonia	Plus 4	00000
Enlarged thyroid and aortitis	0	00000
Pneumonia	0	00000
Uremia	Ac*	00000
Cancer, stomach	0	00000
Sudden deafness	0	00000
Diabetes	0	00000
Diabetes	0	00000
Pneumonia	0	00000
Tuberculosis	0	00000
Rheumatism	0	00000
Nephritis	C 2*	00000
Nephritis	0	00000
Diabetes	0	00000
Pneumonia	0	00000

* Plus 4, all antigens; C plus, cholesternized antigen only; Ac, anticomplementary.

duced in mathematical proportion, may vary from time to time, and may show a selective preference for various antigens.

It demonstrates anew the unlikelihood of devising a complement-fixation technic which will be infallible at all times.

A study of Table 4 shows at a glance the extreme delicacy of the new technic, its flexibility and its decided advantage as a means of regulating and estimating the efficiency of treatment.

By this method far fewer negatives will be obtained, but when obtained they will be of far greater value. As a result, treatment when checked by this method will be likely to be more prolonged and more adequate and the ultimate results more gratifying.

In Table 5 are shown the results in conditions other than syphilis. A large number of hospital serums were, naturally, from a variety of

6. Thaysen, T. E. H.: Spontaneous Variations in the Wassermann Reaction, Acta med. Scandinav. **55**:281 (June 17) 1921.

conditions other than syphilis, but only those are noted in which false positives are known to be occasionally obtained by methods in ordinary use.

It will be seen that the Kolmer modification gave consistently negative results, a further enhancement of the value of the method and an added point in its favor.

In Table 6 are grouped the results of tests on the blood from twenty-three umbilical cords. One was cholesterin-plus by the routine method, the mother and father being Wassermann negative by the same technic. By the Kolmer method the same serum was negative. The blood from three cords was positive to the Kolmer modification, in only one of which was clinical or other corroborative evidence obtainable.

TABLE 6.—RESULTS OF TESTS OF BLOOD FROM TWENTY-THREE UMBILICAL CORDS

Number	Routine	Kolmer	Remarks
3922	C 4	00000	Mother and father negative by both methods; no history
4342	0	00000	
5721	0	44000	No history; mother and father not tested
6077	0	00000	
6157	0	00000	
6226	0	Ac	
6247	0	011000	No history; mother and father not tested
6290	0	00000	
6413	0	00000	
6468	0	00000	
6555	0	00000	
6789	0	00000	
6971	0	00000	
7102	0	00000	
7213	0	00000	
7235	0	40000	History positive; mother treated with neo-arsphenamin and mercury; child apparently healthy
7334	0	00000	
7397	0	00000	
7469	0	00000	
7490	0	00000	
7597	0	00000	
7619	0	00000	
7688	0	00000	

As has been recorded elsewhere,[7] the reliability and usefulness of the Wassermann reaction as conducted on the cord blood as an indication of syphilitic infection has been the subject of some discussion. The composite data of various investigators has shown that the results of the Wassermann reaction in pregnancy must be interpreted with great care, and that the cord blood is especially prone to give fallacious results when tested by methods in common use. In view of the fact, however, that the cord blood specimen is the most easily obtained, and that, except under the most ideal conditions, when it is possible to examine the mother and father as well as the child, this method of

7. Kilduffe, R. A.: The Clinical Evaluation of the Wassermann Reaction, Arch Dermat. & Syph. **6**:147 (Aug.) 1922. The Wassermann Reaction in Its Relation to Prenatal and Congenital Syphilis, Am. J. Med. Sc., to be published.

investigation will always be used to a greater or less degree, it is of decided interest to note the results of the Kolmer modification in even this small series.

The number of specimens is, of course, too small to allow any conclusions, but the results obtained indicate at least the advisability of an extensive trial of the method in obstetric cases which, in all probability, will give results tending to further enhance the value of the method and present added testimony to its general usefulness.

In view of the fact that, in the present series in toto, evidence tending to substantiate a positive finding was obtained in a high propor-

TABLE 7.—Results of Spinal Fluid Examinations

Number	Routine	Kolmer	Remarks
3101	Plus 4	44000	History positive; diabetes; fluid bloody
3163	0	00000	Recurring iritis; blood negattive
3297	C 4	40000	History negative; colloidal gold negative; cells 6
3293	C 4	40000	History negative; colloidal gold 1000000000
3794	Plus 4	44444	History positive; cells 64; colloidal gold 2342341000
3374	0	00000	History positive; cells 6; colloidal gold 1000000000
3393	0	00000	History and colloidal gold negative
3525	0	00000	History and other findings negative
3747	0	00000	History and other findings negative
4062	C 4	44100	Bloody; history negative
4139	0	00000	History negative; colloidal gold negative; cells 6
5582	Plus 4	44444	History positive; blood plus 4; colloidal gold 3222211000; cells 40
5658	0	00000	History negative; cells 19; colloidal gold 1210000000
5659	0	00000	Cells 8; encephalitis; colloidal gold negative
6271	Plus 4	44444	History positive; cells 40; colloidal gold 322221100
6282	0	00000	Cells 19; colloidal gold 121000000; history negative
6435	0	44400	Bloody; no history; symptoms relieved by mercurial treatment
6922	Plus 4	44444	History of chancre 25 years previously; cells 6; colloidal gold 1210000000; gumma (?) abdomen; relieved by antisyphilitic treatment; blood negative
6764	0	44444	History positive; cells 28; colloidal gold 2333430000
6944	Plus 4	44441	History positive; cells 128; colloidal gold 5555554300
7011	0	00000	Cells 10; colloidal gold negative; puerperal sepsis
7030	0	00000	Encephalitis; cells 16; colloidal gold negative
7032	0	00000	Cells 16; colloidal gold 1100000000; gives history of having had three chancres (?)
7450	C 4	00000	Sells 104; colloidal gold 4455555000; chancre 10 years previously
7597	0	00000	Cells 16; colloidal gold 3345544540; history negative; symptoms suggestive of cerebrospinal syphilis
5917	Plus 4	444100	Colloidal gold 555432110; history positive; chancre 15 years previously

tion of cases, the results obtained with these few cord bloods are, at least, of highly suggestive value.

In Table 7 are shown the results of spinal fluid examinations. Most of these fluids were examined because of known or suspected syphilis and a high proportion of positive results was looked for, an expectation amply verified.

With the routine method ten of twenty-five fluids, or 40 per cent., gave a positive reaction in varying degree. There were, however, two cases (6435, 6764) positive to the Kolmer modification but negative to the routine method, in one of which the only finding suggestive of

syphilis was a prompt symptomatic response to mercurial treatment, the other (6764), presenting a positive history and classical cytologic and colloidal gold findings.

One case (7450) with suggestive cytologic and colloidal gold findings and a positive history was negative to the Kolmer modification and positive to the routine test. This is in conformity with findings already referred to and their possible explanation.

The final balance shows twelve or 48 per cent. positive by the Kolmer modification, a gain of 8 per cent.

It will be noted that the phenomenon of stronger reactions in Tube 2 containing a lesser amount of fluid than in Tube 1 did not occur in this small series of spinal fluids and, further, that the strength and degree of fixation could be definitely and graphically set down.

Of some interest are the results in a small series of cases tested when the primary lesion was in its early stage, as shown in Table 8.

In these cases the Kolmer modification picked up the reagin as early as in three and four days, when the routine method was still negative. In other instances, when a cholesterin-positive was obtained

TABLE 8.—RESULTS OF TESTS IN EARLY LESIONS

Age of Lesion	Routine	Kolmer
4 days	0	44100
7 days	C 4	40000
7 days	C 4	44000
5 days	C 4	44120
10 days	C 4 A 2	44400
3 days	0	10000

with the routine method, a distinct variation in the reaction to infection was vividly shown by the Kolmer modification.

In Table 9 are a group of cases of decided interest: serums negative with the routine method but positive by the Kolmer modification. Of 111 such cases, one was a spinal fluid from a known case of syphilis, two were cord bloods without history of syphilis, tests of the mother and father direct not being obtainable; in forty-nine there was definite knowledge of syphilitic infection, many being cases under treatment; and fifty-one were specimens obtained from prostitutes in whom syphilis is a not remote possibility.

In the total series of 1,014 serums, therefore, approximately 10 per cent. additional positives were obtained by the Kolmer modification, in 50 per cent. of which definite evidence of syphilis was obtainable with strong presumptive evidence as to the correctness of the findings in the remaining 50 per cent.—results which speak for themselves.

In view of the strong efforts being made at present toward the control and eradication of venereal infections by health departments, it is of striking significance to note that here were fifty-one prostitutes

TABLE 9.—Cases Negative with Routine Technic But Positive with Kolmer

Number	Routine	Kolmer	Remarks
3007	0	44000	Prostitute
3142	0	44000	Prostitute; syphilis 5 years previously
3165	0	44420	Prostitute; no history
3264	0	44000	Prostitute; history positive; spinal Wassermann plus 4
3482	0	40000	Syphilis, under treatment
3552	0	44200	Prostitute; no history
3883	0	44440	Syphilis, under treatment
4073	0	11000	Syphilis, under treatment
4192	0	44444	Syphilis, under treatment
4195	0	44400	Prostitute; no record
4217	0	01120	Prostitute; no record
4335	0	01100	Syphilis, under treatment
4236	0	44440	Syphilis, under treatment
4253	0	44400	Syphilis, under treatment
4342	0	44000	Cord blood; no history
4501	0	44000	Prostitute; no record
4709	0	41000	Syphilis, under treatment
4798	0	44400	Prostitute; no history
4799	0	44400	Wife is prostitute and has syphilis
4868	0	44400	Prostitute; has had previous Wassermanns (4), all negative to routine technic; no history or lesions
545	0	10000	Syphilis, under treatment
5073	0	44000	Alopecia; adenopathy; sore throat; gonorrhea
5079	0	44000	Cohabits with previous patient; no history; prostitute
487	0	44400	Syphilis, under treatment
462	0	44000	Syphilis, under treatment
463	0	44000	Syphilis, under treatment
5143	0	44100	Prostitute; gonorrhea; no history of syphilis
5172	0	44000	Had prevous plus 4 test by routine technic; prostitute
5173	0	44100	Prostitute; treated syphilis; 10 neo-arsphenamin
5174	0	44000	Runaway; lives with prostitute under quarantine for syphilis
5234	0	44400	Prostitute
5235	0	44400	Syphilis, under treatment
5236	0	44000	Syphilis, under treatment
5347	0	40000	Syphilis, under treatment
5479	0	44000	Prostitute; no hstory
5481	0	40000	Syphilis, under treatment
5313	0	40000	Syphilis, under treatment
5513	0	40000	Prostitute; husband has plus 4 spinal fluid
5522	0	40000	Has been treated for syphilis
408	0	44000	Syphilis, under treatment
5590	0	44000	No record
5593	0	44000	Prostitute; no record
5595	0	40000	No history
5600	0	44000	No history; prostitute
5601	0	44000	Prostitute; no history
5603	0	44000	Amateur prostitute; no history
5515	0	44000	Prostitute; no history
5683	0	44000	Prostitute; no history
5691	0	41000	Prostitute; no history
5745	0	42000	Prostitute; no history
5782	0	43000	Prostitute; no history
5807	0	43000	Prostitute; no history
5823	0	44000	Syphilis, under treatment
511	0	40000	Syphilis, under treatment
6075	0	12000	Prostitute; no history
6076	0	44100	Syphilis, under treatment
532	0	44100	Syphilis, under treatment
536	0	10000	Syphilis, under treatment
539	0	22000	Syphilis, under treatment
6467	0	10000	No history
6505	0	44000	Prostitute; no history
5511	0	44400	Prostitute; no record
6513	0	44000	Prostitute; no history
6519	0	44000	Prostitute; no record
6520	0	41000	Prostitute; no history
6521	0	41000	Prostitute; no history
6522	0	42000	Prostitute; no history
6526	0	41000	Prostitute; no history
6529	0	41000	Prostitute; no history
6531	0	42000	Prostitute; no history
6566	0	44000	No history
6581	0	44200	Prostitute; no history
6583	0	44400	Prostitute; no history
6584	0	44000	Syphilis, under treatment

TABLE 9.—Cases Negative with Routine Technic But Positive with Kolmer—(*Continued*)

Number	Routine	Kolmer	Remarks
6588	0	44000	No history
6624	0	04400	Prostitute; no history
6649	0	04400	Prostitute; no history
6651	0	40000	Prostitute; no history
6694	0	40000	Prostitute; syphilis
6435	0	44440	Spinal fluid syphilis
6732	0	41000	Prostitute; no history
6736	0	44000	Prostitute; no history
6738	0	04200	Prostitute; no history
6741	0	44320	Prostitute; no history
6786	0	44000	Syphilis, under treatment
6841	0	40000	Syphilis, under treatment
6858	0	02000	Prostitute; no history
7023	0	442100	Prostitute; no history
7035	0	44431	Prostitute; no history
7052	0	44410	Prostitute; no history
7074	0	44100	Prostitute; no history
7127	0	44000	Prostitute; no history
7213	0	40000	Cord blood; syphilis, under treatment
7217	0	40000	Prostitute; no history
7249	0	44440	General adenopathy; prostitute
7251	0	43210	General adenopathy; four miscarriages
7259	0	44440	Prostitute; no history
7309	0	44400	Neurosyphilis
7311	0	44000	Prostitute; no history
7332	0	44000	Prostitute; no history
7333	0	42000	Prostitute; no history
7380	0	40000	Syphilis, under treatment
7383	0	44400	Syphilis, under treatment
7407	0	44311	Syphilis, under treatment
607	0	44410	Syphilis, under treatment
7533	0	44440	Syphilis, under treatment
609	0	444100	Syphilis, under treatment
7723	0	44444	General adenopathy; knee reflexes absent; no history
1	0	12110	Cord blood; no history
173	0	10000	Syphilis, under treatment
194	0	44100	Syphilis, under treatment

all released from quarantine on the basis of a negative Wassermann test by a technic comparable to those in common use, many of whom, if not all, it is highly reasonable to suppose were infected with syphilis. Further comment seems unnecessary except to say that if the Kolmer modification were adopted by municipal laboratories charged with the study and control of venereal diseases, a much larger proportion of this element of the population will be held in quarantine and under control than is now the case.

Of no less interest are the thirty-one serums grouped in Table 10—all positive to the routine method and negative by the Kolmer modification.

In fourteen of these there was a definite history of syphilis; one serum was from a case of pneumonia in the febrile stage, in which non-specific fixation of complement is known occasionally to occur, and the remainder are cholesterin positive serums in which a history of syphilis was not obtained.

These findings again demonstrate the fallacy of relying on a single negative reaction by any technic yet devised as infallible evidence of the absence of syphilitic infection at any time in any given stage of the disease, and also demonstrate the relative infrequency with which such false negatives occur with the Kolmer modification.

Table 11 shows results by the Kolmer modification with ninety-one cholesterin-plus serums. In sixty-four, or 70 per cent., both tests agreed, and of these sixty-four cases, forty-three were known to be syphilitic, many being cases of persons under treatment; in ten no data was obtainable, and eleven were prostitutes in whom the possibility of syphilis cannot be overlooked.

The high percentage of agreement between the two methods is of interest as affecting the question of the reliability of cholesterin-plus findings, a factor of interest because the new antigen used in the

TABLE 10.—CASES POSITIVE BY ROUTINE TECHNIC BUT NEGATIVE BY KOLMER MODIFICATION

Number	Routine	Kolmer	Remarks
2050	C 2	00000	No history
2051	Plus 4	00000	Known syphilitic; dark field positive
3041	C 2	00000	No history of syphilis
2068	C 4	00000	No history of syphilis
3238	C 4	00000	Syphilis, under treatment
3297	C 4	00000	Spinal fluid: cells 6; colloidal gold negative; no history
3349	C 4	00000	No record
3356	Plus 4	00000	Primary lesion present
3403	C 4	00000	Nasal lesion clearing up under antisyphilitic treatment; roentgenogram suggestive of syphilis; history negative
3686	C 4	00000	Prostitute; has had previous plus 4
4046	C 4	00000	Syphilis, under treatment
447	C 4	00000	Syphilis, under treatment
4441	C 4	00000	Syphilis, under treatment
4483	Plus 4	00000	Pneumonia; febrile stage
4579	C 4	00000	Prostitute; syphilis, under treatment
4580	C 4	00000	No history
480	C 4	00000	Syphilis, under treatment
5439	Plus 4	00000	Prostitute; now has annular syphilid; three previous tests plus 4; under treatment
5438	C 4	00000	Prostitute; no record
5735	C 4	00000	No record
5838	C 2	00000	Enlarged thyroid and aortitis; no history
513	C 4	00000	Syphilis, under treatment
523	Plus 4	00000	Syphilis
524	C 4	00000	No record
6597	C 4	00000	Prostitute; no history
7148	C 4	00000	Wife has syphilis
7562	C 4	00000	Syphilis, under treatment
7450	C 4	00000	Spinal fluid from cerebrospinal syphilis; cells 102; colloidal gold 445555530; chancre ten years before
619	C 4	00000	Syphilis, under treatment
49	C 4	00000	Lives with prostitute
104	C 2	00000	No record

Kolmer modification is a cholesterinized antigen, albeit reinforced by the addition of the acetone-insoluble lipoids incorporated in it, and if the standard Wassermann test of the future is to rely on such antigens, it behooves serologists, in general, to come to some agreement as to the reliability of cholesterin-plus reactions in general.

This matter of the specificity of cholesterin-plus reactions has been discussed in a previous communication [3] and the results obtained with the Kolmer modification are in no small measure confirmatory of the conclusions then formulated.

TABLE 11.—CHOLESTERIN-PLUS SERUMS

Number	Routine	Kolmer	Remarks
2050	C 2	00000	No record
2052	C 2	44210	No record
2072	C 4	00000	Prostitute; treated syphilis
3041	C 2	00000	No record
2088	C 4	00000	Interstitial keratitis; no history
3136	C 4	44000	Treated syphilis
3140	C 4	44000	Prostitute; lost
1514	C 4	41000	Prostitute; lost
3201	C 4	42000	Wife is prostitute and has syphilis
3238	C 4	00000	Syphilis, under treatment
3297	C 4	00000	Treated syphilis
McK. 3	C 4	34000	Treated syphilis
3349	C 4	00000	Prostitute; lost
3362	C 4	20000	Treated syphilis
3403	C 4	00000	Prostitute; lost
3411	C 4	41100	Treated syphilis
3424	C 4	342000	Syphilis, under treatment
3550	C 4	44000	No record
3571	C 4	40000	Prostitute; lost
3579	C 4	44000	Treated syphilis
3723	C 4	40000	Syphilis, under treatment
3764	C 4	40000	Cerebrospinal syphilis; spinal fluid plus 4 all antigens
3769	C 4	41000	Syphilis, treated
3820	C 4	44000	Prostitute; no record
3899	C 4	44400	Treated syphilis
3922	C 4	44000	Cord blood; mother and father negative to routine method
4046	C 4	00000	No record
4047	C 4	00000	No record
4062	C 4	44100	Spinal fluid, neurosyphilis
4083	C 4	40000	Treated syphilis
4089	C 4	40000	Treated syphilis
4309	C 4	44400	Prostitute; no record
4341	C 4	44000	Syphilis, under treatment
4441	C 4	00000	No record
4500	C 4	44000	Syphilis, under treatment
4515	C 4	44000	No record
4550	C 4	44000	No record
4579	C 4	00000	Syphilis, under treatment
4580	C 4	00000	No history of syphilis
4734	C 4	44400	Neurosyphilis; spinal fluid plus 4 all antigens
4760	C 4	44400	Syphilis, under treatment
4809	C 4	44000	Treated syphilis
4862	C 4	44100	Syphilis, under treatment
4866	C 4	44110	Syphilis, under treatment
4867	C 4	44440	Syphilis, under treatment
4880	C 4	40000	No record
4888	C 4	40000	Prostitute; lost
4906	C 4	40000	Syphilis, under treatmentt
4927	C 4	41000	No record
4932	C 4	40000	Syphilis, under treatment
4935	C 4	40000	Prostitute; no history
5007	C 4	44000	Syphilis, under treatment
5171	C 4	44000	Prostitute; no history
5291	C 4	31000	Syphilis, under treatment
5348	C 4	44440	Adenopathy; husband has syphilis
5458	C 4	00000	Prostitute; no history
5516	C 4	44000	No record
5519	C 4	40000	Neurosyphilis; spinal fluid positive
5962	C 4	44000	Treated syphilis
5742	C 4	44444	Primary lesion still present
5753	C 4	00000	No record; arrested in raid
5814	C 2	44000	No history; lancinating leg pains
5838	C 2	00000	Enlarged thyroid; aortitis
513	C 4	00000	Treated syphilis
522	C 4	40000	Treated syphilis
524	C 4	00000	Treated syphilis
5966	C 4	44000	Chancre three weeks old
6161	C 2	01000	Chancre seven days old
6348	C 4	Ac	Treated syphilis
6349	C 4	Ac	Prostitute; no record
6597	C 4	00000	Prostitute; no record
6740	C 4	44000	Syphilis, under treatment
6785	C 4	44000	Treated syphilis
6948	C 4	44000	Syphilis, under treatment
6931	C 2	44000	Spinal fluid; cells 28; colloidal gold 2333343000; no history
7126	C 4	44400	Syphilis, under treatment
7148	C 4	44400	Treated syphilis
7279	C 4	44430	Prostitute; lost

TABLE 11.—Cholesterin-Plus Serums—(*Continued*)

Number	Routine	Kolmer	Remarks
7280	C 4	44400	Treated syphilis
7381	C 4	44440	Syphilis, under treatment
7562	C 4	00000	Syphilis, under treatment
7450	C 4	00000	Cerebrospinal syphilis; cells 104; colloidal gold 4455555310; chancre ten years previously
7693	C 4	11000	Chancre four weeks ago
619	C 4	44400	Provocative; suggestive history
623	C 4	34430	No record
49	C 4	00000	No history of syphilis
52	C 4	44410	Syphilis, under treatment
104	C 2	00000	No record; prostitute
110	C 4	44400	Prostitute; no history

SUMMARY AND CONCLUSIONS

The results of tests on 1,014 serums examined in parallel series by a routine method of complement-fixation and by the Kolmer modification of the Wassermann reaction are recorded and the findings tabulated and discussed.

As a result of the study the following conclusions seem warranted:

1. There are no disadvantages militating against the adoption of the Kolmer modification as a standard method of complement-fixation in the serologic diagnosis of syphilis.

2. The method presents the following advantages in favor of its adoption, as compared to methods in common use:

(*a*) It possesses greater delicacy.

(*b*) It presents a greater flexibility and elasticity.

(*c*) Strictly quantitative readings are easily made.

(*d*) Nonspecific fixations were not obtained in this series and are, apparently, extremely rare, if they occur at all.

(*e*) It is equally well adapted to the control of treatment as to the diagnosis of syphilis.

3. The new antigen used in the method is superior in every way to any hitherto devised.

4. As a means of determining the efficiency of treatment the method is far superior to any with which I am familiar, giving fewer negative reactions than by the usual methods, and thus ensuring more protracted and adequate treatment.

5. As far as is indicated by the evidence at hand, a positive reaction by this method constitutes extremely good presumptive evidence as to the presence of syphilitic reagin.

6. The method is not infallible and occasionally fails to detect syphilitic reagin in known cases of syphilis, in this respect being similar to all other technics, *except that such false negative reactions occur with much less frequency.*

7. Absolute reliance as to the absence of syphilitic reagin at a given time cannot be placed on the results of a single negative reaction by any method of complement-fixation yet devised.

8. In early primary syphilis the Kolmer modification gives earlier and stronger results than routine methods.

9. The results with this method are in close agreement with the clinical findings in a high percentage of cases.

10. It is a strictly quantitative method and as such better adapted to the study of treated syphilis.

11. It appears to be eminently worthy to supercede and supplant the methods now in common use.

12. It presents by far the most acceptable technic yet proposed for adoption as a standard method and as such should be subjected to extensive, exhaustive and impartial trial and study.

THE SPECIFICITY OF CHOLESTERINIZED ANTIGENS IN THE SEROLOGIC DIAGNOSIS OF SYPHILIS

SECOND COMMUNICATION *

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In a previous communication concerned with this subject,[1] attention was directed to the importance of this question and its thorough investigation was urged.

There are few laboratories in which cholesterinized antigens do not play some part in the serologic diagnosis of syphilis, either forming a part of a multiple antigen battery or even constituting the sole standard by which the positiveness of the reaction is to be gaged.

As noted elsewhere,[2] the problem is one well worthy of, and even compelling, the attention of both serologist and clinician, for its satisfactory solution depends not on either alone but on the combined efforts of both.

It is worthy of comment, and a hopeful augury, to note the gradual eradication, in the discussion of syphilis, as of other conditions, of the tendency to discuss the laboratory and the clinical angles of the problem as more or less separate entities; for the effect of such an attitude can only be stultifying and obstructive. Only when the mutual dependence of clinician and serologist is recognized and emphasized can either attain their supreme effectiveness in the attack on this or any other of the multitude of problems confronting the earnest student of today.

In syphilis, the problem can be divided into two great sections: its diagnosis and its treatment.

The importance of the first is obvious; of no less importance is the question of treatment: how long should it be continued; when may it safely be discontinued?

To all of these, the question of the specificity of cholesterinized antigens is intimately related.

It is, perhaps, rather generally admitted that the treatment of syphilis should be persisted in until a negative reaction is consistently obtained with a cholesterinized extract; it is, therefore, rather with the

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1. Kilduffe, R. A.: Concerning the Specificity of Cholesterinized Antigens in the Serologic Diagnosis of Syphilis, Arch. Dermat. & Syph. **3**:598 (May) 1921.

2. Kilduffe, R. A.: Footnote 1. The Clinical Evaluation of the Wassermann Reaction, Arch. Dermat. & Syph. **6**:147 (Aug.) 1922.

discussion of the interpretation of cholesterin plus reaction from the standpoint of diagnosis that this communication is particularly concerned.

CORRELATION OF CLINICAL AND SEROLOGIC FINDINGS

What is to be the attitude of the clinician and serologist when confronted with such a reaction, in the absence of a positive or suspicious history or of easily discernible clinical findings?

Certain general premises previously laid down [2] may be repeated here:

1. If cholesterinized antigens are to be regarded as frequently prone to give nonspecific or false reactions, then, without question, to make a Wassermann test with these as the sole antigens is a dangerous procedure and one which should not be countenanced by either clinician or serologist.

This is a proposition which it seems difficult to deny; and yet this is the situation which obtains in numerous institutions and laboratories of standing both here and abroad, and this was the technic relied on by the laboratories of both the British and the American expeditionary forces in the World War.

It is inevitable and can be admitted without question that some of the reactions reported must have been weakly positive. Where is the borderline between the specificity and nonspecificity of such reactions? What degree of fixation to cholesterinized antigens is specific and what nonspecific? How is this determined? What are the data on which reliance on such reactions is obtained?

These are all pertinent queries, of interest to patient, clinician and serologist alike, of sufficient importance to demand a concerted attempt at a satisfactory answer.

2. In the unknown case tested for diagnosis, a cholesterinized plus reaction should form the basis of an exhaustive clinical, historical and laboratory study, fortified by repeated serologic blood and possibly spinal fluid examinations. Under such circumstances, corroboratory evidence will be obtained in a large percentage of cases.

3. To pass over a cholesterin plus reaction, in the absence of fixation with other antigens, as generally nonspecific and of no moment is an attitude certainly not justified by the data available.

It is unfortunate that, in the matter of diagnosis in the doubtful case, the clinician and the serologist are still some distance apart. The opinion of the serologist as to the interpretation of his examination is too infrequently sought, and still more infrequently is he in possession of sufficient clinical as well as laboratory data on which to formulate such an opinion.

The division of physicians into clinicians and pathologists should be merely an arbitrary one, denoting the particular phases of medicine in which each has a compelling interest. The ability and skill of the clinician is best founded on a broad knowledge of the pathology of the conditions he essays to treat; the pathologist finds his greatest usefulness when he regards and interprets his findings in the light of their clinical application; neither can work in separate fields or do good work in the same field if they elect to remain apart and solitary.

It is impossible for either to make of himself a Robinson Crusoe; inevitably, he will find on his solitary strand the footprints of the other.

It is unfortunate that the clinician is too often content to leave in abeyance the question of the competence of the serologist to whom he refers his examinations; and too often is he satisfied with a negative or positive report from the laboratory, while remaining in abysmal ignorance of the identity of the worker or the reliability of his technic. And far too often is the result of a single Wassermann report deemed sufficient basis for definite diagnostic and prognostic assertions.

Many of the reports thus accepted without cavil are based on reactions to cholesterinized antigens alone and, if this is the case, the clinician should be so informed, and he should be possessed of data on which to formulate a conclusion.

VARIATIONS IN TECHNIC

The question of cholesterinized antigens cannot be evaded by the adoption of a standardized technic, a consummation devoutly to be wished.

So far, but two worthy of note have been proposed, one by Hinton,[3] in which three antigens are used: two different cholesterinized extracts of human heart and one cholesterinized extract of guinea-pig heart—thus relying entirely on cholesterinized antigens. With this method, I have had no experience.

Kolmer [4] has recently published a technic based on an extensive and long-continued series of studies, which has been tested in these laboratories in a series of 1,014 cases, a report of which is to be published.

In this method, which is a strictly quantitative one, but one antigen is used, a polytropic cholesterinized extract of beef heart to which is added the acetone-insoluble lipoids of the same extract. A careful trial of this method has shown a remarkable degree of delicacy, specificity and agreement with the clinical findings, and the technic seems eminently worthy for adoption as a standard.

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3. Hinton, W. A.: A Standardized Technic for Performing the Wassermann Reaction, Am. J. Syphilis **4**:598 (Oct.) 1920.

4. Kolmer, J. A.: A New Complement-Fixation Test in Syphilis Based upon the Results of Studies in the Standardization of Technic, Am. J. Syphilis **6**:1 (Jan.) 1922.

It seems apparent that the standardized technic of the future will certainly involve the use of cholesterinized antigens, and some conclusion as to their reliability must, therefore, be agreed on.

This can only be attained by the careful collection and analysis of statistics concerned with cholesterin plus reactions, and by the cooperation of clinician and serologist. All such cases should be carefully investigated as to the presence or absence of clinical signs, the history and the results of further serologic tests.

STUDY OF CASES REACTING TO CHOLESTERIN ANTIGENS

In the present communication, such a study of 159 cases reacting to cholesterin antigens has been attempted.

The cases were collected from those in which reactions occurred in routine Wassermann tests made in these laboratories during the past year (May, 1921, to May, 1922), and were not selected in any way.

Whenever a cholesterin plus reaction occurred, an effort was made to secure all the history and clinical data possible and, if possible, further specimens for examination.

In many of these cases of persons held by the morals court, specimens were secured through Dr. A. H. Eggers, county medical inspector of Allegheny County, Pa., to whom acknowledgment is due for historical data and subsequent specimens. In not a few of these cases, the subsequent serologic examinations were made in other laboratories, using various modifications of technic. The remainder of the series were cases from the wards of the Pittsburgh Hospital and from patients sent to the laboratory for examination.

The technic of the Wassermann reaction as employed in this series has been detailed elsewhere.[5] In brief, it consisted in the employment of a triple antigen battery (cholesterinized extract of human heart, acetone-insoluble lipoids of human heart, and alcoholic extract of syphilitic fetal liver), with two units of titrated complement and fixation in the cold water bath at from 2 to 4 C.

The accompanying table presents the cases and the results obtained in detail.

Including repeat tests, a total of 213 Wassermann tests were made.

It will be noted that, of 159 cholesterin plus reactions, a history of syphilis or clinical evidence of syphilitic infection was obtained in eighty, or approximately 50 per cent.

These cases, on investigation, were found to be either cases of known syphilis under treatment, cases with a history of syphilis

5. Kilduffe, R. A.: The Kolmer Modification of the Wassermann Reaction: A Report of Its Trial in a Series of 1,014 Cases, Arch. Dermat. & Syph., this issue, p. 709.

Results of Wassermann Test in a Series of Unselected Cases

Case	Wassermann	Comment	Other Tests
1	C 4 *	Treated syphilis	Two negative
2	C 4	Prostitute; lost	None
3	C 4	Treated syphilis	None
4	C 4	Cohabits with prostitute; no history	One negative
5	C 4	Prostitute; no history	C 4; C 4 A 3 †
6	C 4	Treated syphilis	Plus 4 ‡
7	C 4	Prostitute; no history	C 4 A 1
8	C 4	Prostitute; no history	None
9	C 4	Prostitute; no history	None
10	C 4	Treated syphilis	C 4
11	C 4	Prostitute; no history	Two negative
12	C 4	Treated syphilis	None
13	C 4	Treated syphilis	None
14	C 4	Prostitute; no history	None
15	C 4	Prostitute; no history	C 3; C 4; negative
16	C 4	Treated syphilis	None
17	C 4	Wife has syphilis; plus 4 Wassermann reaction	Negative
18	C 4	Prostitute; no history	Negative
19	C 4	Prostitute; treated	None
20	C 4	Prostitute; treated	Two negative
21	C 4	Prostitute; treated	Two negative
22	C 4	Treated syphilis	Negative
23	C 4	Treated syphilis	Negative
24	C 4	Prostitute; lost	None
25	C 4	Prostitute	Plus 4
26	C 4	Lesions present	None
27	C 4	Husband infected	None
28	C 4	Prostitute	Plus 4
29	C 4	Prostitute, treated syphilis	None
30	C 4	Prostitute; no history	Plus 4
31	C 4	Treated syphilis	None
32	C 4	Prostitute; no history	None
33	C 4	Prostitute; treated syphilis	Two negative
34	C 4	Treated syphilis	Negative
35	C 4	Cohabits with prostitute	Spinal fluid plus 4
36	C 4	Treated syphilis	C 4
37	C 4	Prostitute; lost	None
38	C 4	Prostitute; lost	None
39	C 4	Prostitute; lost	None
40	C 4	Prostitute; no history	Negative
41	C 4	Treated syphilis	None
42	C 4	Prostitute; lost	Anticomplementary
43	C 4	Prostitute; lost	None
44	C 4	Visible lesions; treated	None
45	C 4	Prostitute; lost	None
46	C 4	Prostitute; lost	None
47	C 4	Prostitute; lost	None
48	C 4	Treated syphilis	C 4
49	C 4	Prostitute; lost	None
50	C 4	Prostitute; lost	None
51	C 4	Prostitute; lost	None
52	C 4	Treated syphilis	C 4 A 4; C 4
53	C 4	Glandular involvement; lost	None
54	C 4	Treated syphilis	None
55	C 4	Prostitute; lost	None
56	C 4	Prostitute	C 4 A 4; C 4; C 4
57	C 4	Treated syphilis	None
58	C 4	Treated syphilis	None
59	C 4	Prostitute; no history	Plus 4; plus 4
60	C 4	Secondary infection	None
61	C 4	Treated syphilis	None
62	C 4	Prostitute; lost	None
63	C 4	Treated syphilis	Plus 4
64	C 4	Prostitute; no history	Plus 4
65	C 4	Prostitute; lost	None
66	C 4	No history	Plus 4; negative; negative
67	C 4	Prostitute; lost	None
68	C 4	Treated syphilis	None
69	C 4	Chancre present	None
70	C 4	No history	None
71	C 4	Cohabits with prostitute	Plus 4
72	C 4	Prostitute; lost	None
73	C 4	Known syphilis	Died
74	C 4	Prostitute; no history	C 4; C 4; spinal fluid plus 4
75	C 4	Prostitute; no history	"Delayed negative"
76	C 4	Prostitute; no history	None
77	C 4	Treated syphilis	None
78	C 4	Prostitute; no history	None
79	C 4	Syphilis under treatment	Lost
80	C 4	Prostitute; lost	None
81	C 4	Prostitute; treated syphilis	Plus 4

RESULTS OF WASSERMANN TEST IN A SERIES OF UNSELECTED CASES—(*Continued*)

Case	Wassermann	Comment	Other Tests
82	C 4	Prostitute	Spinal fluid plus 2
83	C 4	Treated syphilis	C 3 A 2
84	C 4	Treated four years ago	None
85	C 4	No history	None
86	C 4	No history	None
87	C 4	No history	None
88	C 4	No history	None
89	C 4	Known syphilis; son has congenital syphilis with plus 4 Wassermann reaction	None
90	C 4	Chancre one month ago	None; lost
91	C 4	Prostitute; lost	None
92	C 4	Prostitute; lost	None
93	C 4	Treated syphilis	C 3; C 4
94	C 4	Prostitute; no history	Plus 4
95	C 4	Treated syphilis	"Positive"
96	C 4	Treated syphilis	None
97	C 4	Prostitute; lost	None
98	C 4	Prostitute; treated	Negative
99	C 4	Wife had syphilis	None
100	C 4	Treated syphilis	None
101	C 4	Treated syphilis	C 4 A 4
102	C 4	Prostitute; lost	None
103	C 4	Chancre one month ago	None; lost
104	C 4	Treated syphilis	None
105	C 4	Treated syphilis	None
106	C 4	Prostitute; lost	None
107	C 4	Prostitute; no history	Plus 4
108	C 4	Prostitute; lost	None
109	C 4	Chancre present	Lost; none
110	C 4	Prostitute; no history	None
111	C 4	History doubtful	None
112	C 4	Treated syphilis	None
113	C 4	Treated syphilis	None
114	C 4	Treated syphilis	None
115	C 4	Treated syphilis	None
116	C 4	Treated syphilis	None
117	C 4	Treated syphilis	None
118	C 4	Treated syphilis	None
119	C 4	Treated syphilis	None
120	C 4	Treated syphilis	None
121	C 4	Treated syphilis	None
122	C 4	No history	None
123	C 4	No history	None
124	C 4	No history	None
125	C 4	No history	None
126	C 4	No history	None
127	C 4	No history	None
128	C 4	No history	None
129	C 4	No history	None
130	C 4	No history	None
131	C 4	No history	None
132	C 4	No history	None
133	C 4	No history	None
134	C 4	No history	None
135	C 4	No history	None
136	C 4	Prostitute; no history	None
137	C 4	Prostitute; no history	None
138	C 4	Lesions present	None
139	C 4	Lesions present	None
140	C 4	Treated syphilis	None
141	C 4	Treated syphilis	None
142	C 4	Treated syphilis	None
143	C 4	Treated syphilis	None
144	C 4	Treated syphilis	None
145	C 4	Treated syphilis	None
146	C 4	Treated syphilis	None
147	C 4	Treated syphilis	None
148	C 4	Treated syphilis	None
149	C 4	Treated syphilis	None
150	C 4	Treated syphilis	None
151	C 4	Treated syphilis	None
152	C 4	Treated syphilis	None
153	C 4	Treated syphilis	None
154	C 4	Treated syphilis	None
155	C 4	Treated syphilis	None
156	C 4	Treated syphilis	None
157	C 4	Treated syphilis	None
158	C 4	Treated syphilis	None
159	C 4	No record	None

* Plus 4 to cholesterinized antigen only.
† C 4 A 4: Plus 4 to cholesterinized antigen and to acetone-insoluble lipoids.
‡ Plus 4: Plus 4 to all antigens.

previously treated, or cases in which early or late clinical manifestations of syphilis were demonstrable.

In seven cases, a suggestive history ("cohabits with prostitute," "lives with infected prostitute," "husband or wife has syphilis," etc.) was elicited, thus providing presumptive evidence of syphilitic infection. Including these, there is a total of eighty-seven, or 54.7 per cent., in which syphilis could be proved or its possibility not denied.

There were fifty serums from admitted professional prostitutes who, naturally, gave a negative history or concerning whom, for one reason or another, no data could be had; many of these were examined but once, and it is debatable how many could have been proved infected if more exhaustive examinations could have been obtained.

In this connection, it is interesting to note that, of a total of ninety-one professional prostitutes examined, twenty-five, or 26 per cent., were definitely shown to be syphilitic.

In twenty-one cases of the series, no data of any kind were obtainable nor was a repetition of the test possible.

It is, of course, realized that this series is too small to permit of exhaustive deductions or analysis, and it is obvious that, for evident reasons, it was not possible to conduct an extended or thorough investigation in any one case. Nevertheless, even this incomplete survey is sufficient to indicate that, in more than 50 per cent. of the persons examined, a cholesterin plus reaction could be shown to be indicative of the presence of syphilitic reagin in the blood. If such reactions are to be looked on as meaningless and of no value, then eighty syphilitic persons would have been overlooked or prematurely discharged from treatment, not a few being professional prostitutes and thus a source of continual danger to the community.

The problem seems an important one and well worthy of extended investigation.

The salient features may be thus briefly expressed:

1. Cholesterinized antigens form a permanent factor in the serologic diagnosis of syphilis.

2. It seems highly probable that the standard Wassermann technic of the future will depend in no small measure on the results of tests against such antigens.

3. Under ordinary circumstances, nonspecific reactions with normal serums are certainly much more infrequent than has generally been supposed, and with a carefully titrated, checked and controlled antigen are rare.

4. Nonspecific fixation by cholesterinized antigens with normal serums (in the absence of lobar pneumonia in the febrile stage, pregnancy, leprosy and yaws), in 100 per cent. or four plus degree, is very rare and infrequent.

5. The cavalier refusal to grant any significance to cholesterin plus reactions in general is an unjustifiable attitude, not supported by available data.

VALUE OF REACTIONS

If a cholesterin plus reaction, in the presence of an early chancre, is a true indication of the presence of syphilitic reagin, what is the status of the same reaction when the presence of the chancre is not known? If treatment cannot be safely discontinued in the persistent presence of a cholesterin plus reaction, what is to be done when the syphilitic person denies or presents no obvious signs of previous infection or treatment?

It would seem of the highest importance for both clinician and serologist to evolve a concerted opinion as to the general reliability and specificity of these reactions and to determine the exact degree of dependability to be assigned to them.

It is not for the clinician alone to determine. Too often he is not sufficiently familiar with, or, what is worse, not sufficiently interested in, matters of technic to bestir himself in an endeavor to ascertain the competence of his serologist or the dependability of his technic.

Nor is it a problem for the serologist alone; if he is concerned only with the serum and his pipets and test tubes, his information and his avenues of investigation are limited to and imprisoned within the walls of his laboratory.

It is a problem necessitating both clinical and laboratory investigations, not as separate but as united forces; investigation by clinicians sufficiently familiar with the theory and mechanism of the methods of investigation they employ, and by serologists in sufficiently close contact with the clinical sides of their work, to properly evaluate their findings.

When confronted with the borderline case, it is only when both are met on the neutral ground of consultation that results of value will be obtained.

Ponderous arguments as to whose shall be the prerogative and glory of the diagnosis are of little moment. Syphilis—or any other condition—cannot be segregated into widely separated zones of diagnosis and clinical findings; the clinician must be sufficiently a pathologist to apply properly the studies of the laboratory; the pathologist must be sufficiently a clinician to properly interpret the results of his investigations, and both must cooperate to properly correlate and evaluate the results of their combined investigations.

CONCLUSIONS

1. Cholesterin plus reactions cannot be safely disregarded as generally nonspecific.

2. The problem of the specificity of cholesterinized antigens should be exhaustively investigated.

3. The occurrence of a cholesterin plus reaction constitutes strongly presumptive evidence of the presence of syphilitic reagin and necessitates a further and an exhaustive examination—clinical, historical and laboratory.

EXPERIENCE WITH THE KOLMER QUANTITATIVE COMPLEMENT FIXATION TEST FOR SYPHILIS *

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The new quantitative technic for complement fixation in syphilis, as recently published by Dr. John A. Kolmer,[1] has been employed by us since November, 1921, in the examination of 362 specimens of serum from 329 patients. The Dermatologic Research Institute of Philadelphia examined 100 of these serums in collaboration with this laboratory, employing both their old method and the new Kolmer technic. The serums of these 100 patients were drawn for both laboratories at the same sitting. These serums were all from patients who have been thoroughly studied clinically. In many of them, the diagnosis has been proved in the surgery or at necropsy, and in only a few has there been clinical uncertainty as to the condition present.

The 362 serums may be grouped as follows: positive Wassermann reaction, positive clinically, 136; negative Wassermann, negative clinically, 181; positive Wassermann, negative clinically, fifteen; negative Wassermann, positive clinically, two; syphilitic patients under treatment, with previously strongly positive Wassermann reactions which are now negative, three; and unclassified serums in which the Wassermann reactions were variable on different days, fifteen, all of which were from five patients.

Throughout this series, the usual good technical care was exercised and all serums were examined in our laboratory by the same technician. The new technic was exactly adhered to in every detail. The old method (A) as employed in this laboratory consists of a water-bath fixation technic, employing 0.5 c.c. of a titrated 0.4 cholesterinized human heart antigen, two units of titrated antisheep amboceptor, 0.5 c.c. of a 1:10 dilution of guinea-pig complement, 0.5 c.c. of a 1:20 suspension of sheep cells and 0.2 c.c. of desensitized patient's serum, with a sharply adjusted hemolytic system. This we considered in our hands a sensitive technic. An acetone insoluble antigen with otherwise the same reagents was employed as a control (B). A second control consisted of a 0.2 cholesterolized lecithinized beef heart antigen, pre-

* From the Virginia Mason Hospital Laboratory.

1. Kolmer, J. A.: Studies in the Standardization of the Wassermann Reaction; a New Complement Fixation Test for Syphilis Based upon the Results of Studies in the Standardization of Technique, Am. J. Syphilis **6**:82 (Jan.) 1922.

pared according to the method of Kolmer,[2] with a primary short icebox incubation of four hours (C). The old method, as applied at the Dermatologic Research Institute, employs three antigens, a cholesterinized, an alcoholic syphilitic liver, and an acetone insoluble lipoid.

An analysis of the results of this study leads us to the following conclusion: The new Kolmer quantitative technic has greater sensitivity than our old methods.

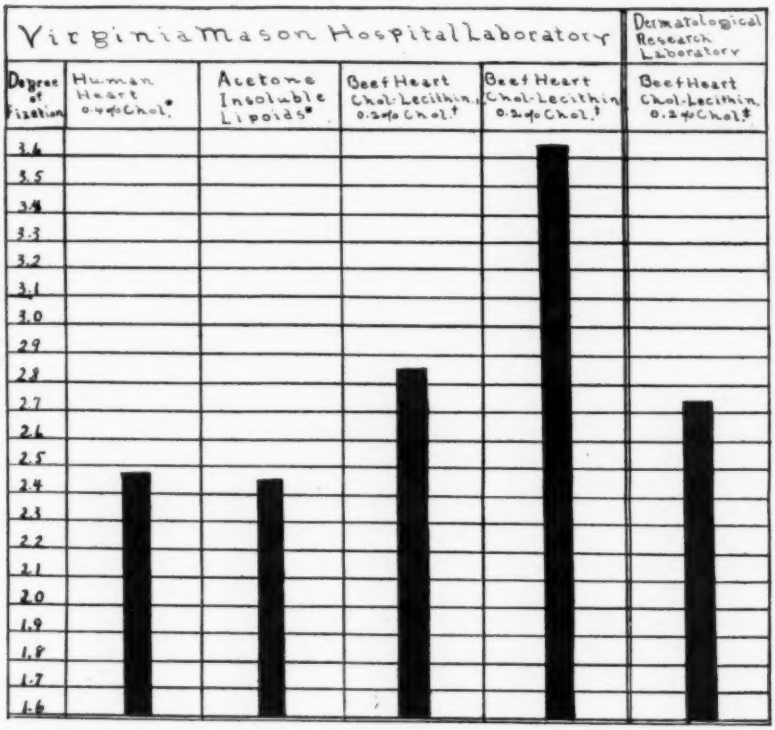

Chart 1.—Degree of hemolysis, clinically positive cases. * Water-bath, one-half hour. † Icebox incubation four hours. ‡ Kolmer quantitative icebox incubation, eighteen hours.

The results with the new technic agreed with the clinical evidence in the clinically positive cases in 97 per cent. in our laboratory and 81 per cent. in Philadelphia. Our old technics agreed in 92 and 83 per cent., respectively. Even the short icebox method agreed in only 93 per cent. The percentages with the old technics are comparatively

2. Kolmer, J. A.: Studies in Standardization of the Wassermann Reaction; a Superior Antigen for Complement Fixation Tests in Syphilis (A Cholesterolized Lecithinized Alcoholic Extract of Heart Muscle), Am. J. Syphilis **6**:74 (Jan.) 1922.

higher because one plus reactions, which are usually considered questionable, are counted as positives, while none of these weak reactions occurred with the new technic. The average degree of hemolysis with the new technic in our laboratory, in this group of the cases, was plus 3.6 and in Philadelphia was plus 2.7. We believe that this low degree of hemolysis obtained in Philadelphia was due to the fact that from eight to fourteen days were consumed on the average in shipment

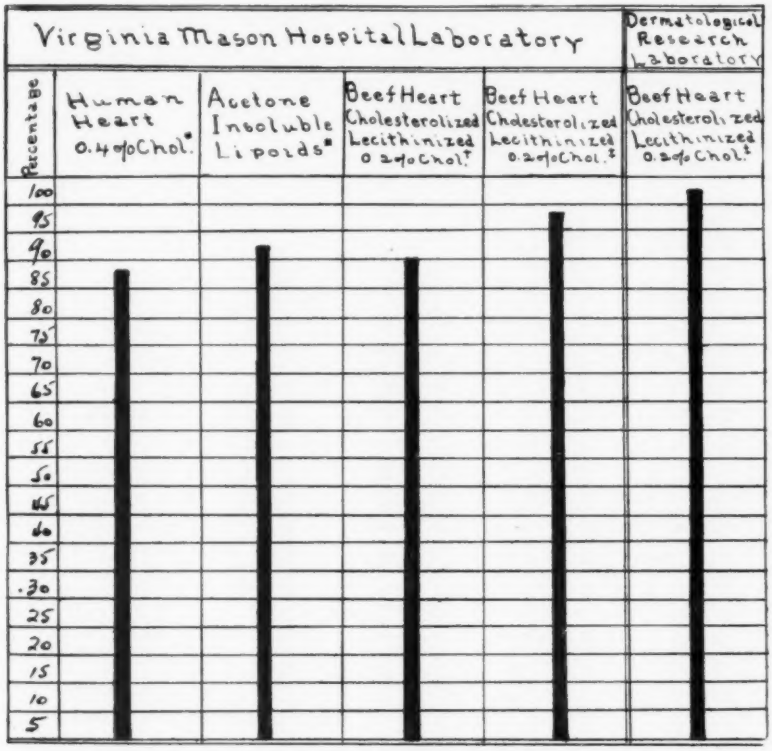

Chart 2.—Percentage agreement with clinical evidence, clinically negative cases. * Water-bath, one-half hour. † Icebox incubation, four hours. ‡ Kolmer quantitative icebox incubation, eighteen hours.

and that many of the serums were deteriorated or showed a weakening of reagin. The average degree of hemolysis with our old technic was plus 2.5 (A) and plus 2.4 (B) respectively, and only plus 2.8 (C) with the short icebox method. It is evident, therefore, that employing the new Kolmer cholesterolized lecithinized antigen, in a short icebox technic, does not give the same high degree of sensitivity as does the new Kolmer quantitative method. Criticism of the new technic, based on any modification of the Kolmer method, is, in our opinion, not dependable. For instance, shortening the primary icebox incubation

TABLE 1.—Clinically Positive Reactions Under Old and New Technic

	Clinically Positive Reactions								
	Virginia Mason Hospital				Kolmer,		Virginia Mason Hospital			
Case	Old			New	New	Case	Old			New
1	4	4	4	44200	44100	69	1	2	3	42100
2	4	4	4	43100	43000	70	4	4	4	42000
3	3	4	3	32100	43000	71	0	0	0	32100
4	3	2	3	42200	30000	72	4	4	4	33000
5	0	0	2	43200	20000	73	1	0	1	40000
6	4	4	4	44000	44000	74	1	2	2	12000
7	1	2	2	44330	42000	75	4	4	4	04000
8	4	4	4	44300	41000	76	4	4	4	44433
9	2	1	3	21000	00000	77	1	2	3	43200
10	3	3	3	33100	40000	78	2	2	3	44000
11	2	2	3	44310	40000	79	4	4	4	44430
12	4	4	4	44210	30000	80	2	2	2	43000
13	1	0	2	32000		81	4	4	4	44430
14	1	1	2	21000	32000	82	4	4	4	44000
15	0	0	0	00000	42000	83	1	2	2	30000
16	0	0	0	20000	44000	84	4	4	4	44000
17	4	4	4	44000		85	4	4	4	44000
18	1	1	2	33000	00000	86	3	3	3	44300
19	2	1	3	41000	00000	87	4	4	4	44300
20	2	3	3	44320	44000	88	0	0	0	22000
21	4	4	4	44430	44100	89	1	2	2	32000
22	1	3	3	44320	44000	90	2	2	2	32000
23	2	4	4	44333	44000	91	.....			30000
24	0	0	0	44200	00000	92	1	1	1	30000
25	3	3	4	43300	43000	93	1	1	1	22000
26	3	2	4	43000	44000	94	2	3	3	42100
27	4	4	4	44200	44000	95	2	2	2	41000
28	4	4	4	44320	A C	96	2	3	2	41000
29	4	4	4	43100	44000	97	4	4	4	44300
30	4	4	4	44330	44200	98	2	2	2	42000
31	2	2	3	42000	44000	99	4	4	4	43000
32	2	3	3	33000	00000	100	1	1	2	42000
33	4	4	4	44100	44000	101	3	2	3	44400
34	4	4	4	44332	10000	102	4	4	4	44442
35	1	1	2	43200	00000	103	3	2	3	44300
36	2	2	3	40000		104	1	2	3	43000
37	1	0	2	31000	00000	105	3	3	4	44300
38	3	2	4	44200	44000	106	0	2	2	33000
39	4	4	4	44100	44000	107	2	2	3	31000
40	2	2	3	42000	42000	108	1	0	2	31100
41	3	2	3	43000	10000	109	2	2	3	43100
42	3	3	3	43000	42000	110	4	4	4	44200
43	4	4	4	43100	44000	111	1	0	2	41000
44	2	1	3	43000	41000	112	1	1	2	42000
45	2	2	2	42000	42000	113	4	4	4	44200
46	1	0	2	31000	42000	114	1	1	1	41000
47	1	1	1	44000	43000	115	3	3	4	44300
48	4	4	4	44200	44000	116	2	3	2	44000
49	3	2	4	44000	44000	117	1	1	1	43000
50	.....			41000	44000	118	2	2	3	31000
51	4	4	4	44300	44100	119	2	2	3	41000
52	4	4	4	44300	00000	120	2	1	2	41000
53	3	3	4	43000	A C	121	4	4	4	43000
54	3	2	3	44300	20000	122	4	4	4	44300
55	1	0	2	44000	44000	123	1	0	1	02000
56	1	1	1	40000	00000	124	2	1	3	03000
57	0	0	0	20000	00000	125	0	0	0	31000
58	4	4	4	44210		126	2	2	3	43200
59	0	0	0	44000		127	2	1	2	44300
60	2	1	2	44200		128	0	0	0	32000
61	2	2	2	43200		129	0	0	0	31000
62	4	4	4	44430		130	4	4	4	44300
63	4	4	4	44300		131	3	3	4	44300
64	4	4	4	44000		132	4	4	4	44300
65	4	4	4	44000		133	4	4	4	44300
66	4	4	4	44320		134	2	2	3	44420
67	4	4	4	44320		135	3	3	3	30000
68	1	2	2	44300		136	4	4	4	43000

to less than twelve hours in the Kolmer technic has proved to be less sensitive than our old technic (C), which employed a cholesterinized antigen and a four-hour icebox primary fixation. The new technic gave stronger reactions in fifty-three of the 136 positive Wassermann and clinically positive cases, while in only three cases was the reaction weaker than with the old technic. More important is the fact that the new technic gave a diagnostically positive reaction in nine of the 136 clinically positive cases in which the old technics gave a negative.

The new Kolmer technic has greater specificity than our old methods.

The results with the new technic agreed with the clinical evidence in the clinically negative cases in 94 per cent. in our laboratory and in 97 per cent. in Philadelphia. Our old technics agreed in 83 per cent. (A) and 87 per cent. (B), respectively, and the short icebox method (C) agreed in 85 per cent. If a false positive does occur with the new technic, the degree of hemolysis is greater than with the old technics.

TABLE 2.—CLINICALLY NEGATIVE, WASSERMANN POSITIVE REACTIONS WITH OLD AND NEW TECHNIC

Clinically Negative Wassermann Positive Reactions								
	Virginia Mason Hospital			Kolmer,		Virginia Mason Hospital		
Case	Old			New	Case	Old		New
1	0	0	0	30000	9	1	2	1	31000
2	0	0	0	43000	00000 10	1	0	1	02000
3	0	0	0	44300	11	2	1	3	03000
4	0	0	0	00000	04210 12	0	0	0	31000
5	1	1	2	43000	13	0	0	0	32000
6	0	0	0	30000	14	0	0	0	41000
7	1	1	2	40000	15	0	0	0	41000
8	1	0	2	23310					

In ten cases with no clinical evidence of syphilis, positive reactions were obtained with the new technic. However, it could not be proved by history or examination that these were not cases of latent syphilis. All the patients had given previous variable Wassermann reactions, and in three of the ten cases in which the serums were checked on different days, the reactions were consistently positive. However, it is possible that some of these reactions were false positives, and they have been considered as such. In compiling the foregoing percentages, there is no more evidence for than against this fact.

In five of the 329 patients, the reactions obtained with their serums, were not consistent on different days, using the new technic. In one case of gastric ulcer, with a positive history of syphilis, and some treatment, a 20000 reaction was obtained; and, two weeks later, a negative. In a second case, with negative clinical findings and no syphilitic history, a 44300 reaction was obtained, followed by two negative reactions about ten days apart. In a third case, with a diag-

nosis of duodenal ulcer and no findings or history of syphilis, a 44300 reaction was obtained in the same run as the second case, followed by two negative reactions about ten days apart. In a fourth case, that of a colored woman in whom the diagnosis was fibroid uterus and who gave a questionable history of syphilis, a 44000 reaction was obtained, followed a week later by a negative reaction, which was followed, in turn, a week later, by a 44300 reaction. In a fifth case, with no diagnosis other than nervous exhaustion and no history or clinical evidence of syphilis, a 04300 reaction was obtained, followed by a negative reaction a week later. In the first and fourth of these cases, the negatives are considered by us to be false, and in the other three cases, the positives are considered to be false, the opinions being based on careful clinical consideration.

TABLE 3.—WASSERMANN VARIABLE REACTIONS WITH OLD AND NEW TECHNIC

	Wassermann Variable Reactions								
	Virginia Mason Hospital				Kolmer,		Virginia Mason Hospital		
Case	Old			New	New	Case	Old		New
1	4	2	4	20000	41000	3	1	1	2	00000
1	0	0	0	00000		4	0	0	0	44000
2	4	4	4	44300		4	0	0	0	00000
2	0	0	0	00000	00000	4	1	1	2	44300
2	1	1	1	00000		5	1	1	2	04300
3	1	1	2	44300		5	0	0	0	00000
3	0	0	0	00000	00000					

The new technic gives in our laboratory a much lower percentage of anticomplementary reactions than the old technics. Only 40 per cent. as many of the 362 serums were anticomplementary with the new technic as with our old technics.

There was total disagreement as to positive or negative reactions in 13 per cent. of the 100 serums examined, both in our laboratory and at Philadelphia. This is high because of changes taking place in the serums during shipment.

The quantitative phase of the new technic is very valuable. The gradation of hemolysis in the five tubes indicates the quantity of reagin present in the serum being examined. Although this is of some value from a diagnostic standpoint, it is of greater importance in cases under treatment. Here it indicates the effect of treatment and acts as an indicator for further therapy.

Certain advantages which stand out prominently in opposition to any criticism that might be made of the new technic have been brought to our attention during the use of it. It is true that the new technic requires more time, and the reports will be somewhat delayed as compared with the old methods, but we believe that this is justified by the greater accuracy of the results obtained. This increased accuracy

should not be sacrificed for a little saving of time and labor. The reason that the sensitivity of our old method rates so high is that, in compiling the percentages, one plus reactions were considered positive in the group of clinically positive cases. In a large number of cases, serums giving one, two or three plus positive reactions with the old technic gave a four plus with the new method. Clearcut and easily read reactions are always obtained. Not over five one or two plus reactions have been obtained with the new technic. As emphasized by the author, it has been our experience that in adjusting the hemolytic system, it is important to use the second tube showing complete hemolysis as the unit of complement instead of the first tube, as is commonly done in methods not employing icebox fixation.

CONCLUSIONS

The new Kolmer quantitative complement fixation test for syphilis differs from our old methods as follows:

1. It shows greater sensitivity.
2. It shows greater specifity.
3. It gives fewer anticomplementary reactions.
4. It is more economical.
5. It requires somewhat more time and labor.
6. The reactions are sharper and more easily read.
7. It has the added value of a quantitative phase.

STUDIES IN THE CHEMOTHERAPY OF FUNGUS INFECTIONS

I. THE FUNGISTATIC AND FUNGICIDAL ACTIVITY OF VARIOUS DYES AND MEDICAMENTS *

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AND

JOHN A. KOLMER, M.D.

PHILADELPHIA

The new science of chemotherapy, which has achieved brilliant success in the attack on certain spirochetal infections, offers a fertile field for research in connection with other parasites. It is possible to produce new chemical compounds which will possess affinities for cocci, bacilli, fungi, etc. In order to pursue fruitful research along these lines, it is desirable that the parasiticide properties of old and known medicaments be investigated and classified.

Modern medicine employs the experimental method in the development of new remedies for infectious diseases in contrast with the empiric method that characterized the prelaboratory period in medicine. There are two lines of approach in investigative work of this character. One is chemically to modify a drug or compound of clinical value in a certain infection and test the various modifications until an enhanced parasiticidal value is obtained. Starting with atoxyl, which possessed trypanocidal power and a perceptible influence in syphilis, Ehrlich and his associates, after a brilliant research, ultimately elaborated arsphenamin.

In conjunction with Dr. Raiziss, we have shown that an organic mercurial compound—sodiumoxymercury orthonitrophenolate— is from five to seven times more inhibitive to the growths of various cocci than mercuric chlorid. Another mercury compound with which we have been experimenting has a strong affinity for bacilli.

The most desirable method of determining affinities is first to employ the compound in the test tube against cultures of various microorganisms. However, as the results in vitro constitute no convincing evidence of the power of a drug in vivo, it is necessary to infect susceptible animals with various parasites and then inject into each animal the compound under investigation.

In dealing with parasites, such as fungi, which attack merely the skin and its appendages, intravenous or constitutional medication appears to be superfluous.

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* From the Dermatological Research Institute.

As far as we have been able to determine, no chemotherapeutic research has hitherto been carried out in connection with infections caused by pathologic molds or fungi. The remedies which are in use for ringworm, tinea versicolor and favus have come into employment as a result of empiricism. The thought has occurred to us that laboratory studies of the fungicidal properties of different medicaments would shed light on the chemical affinity of these drugs for different fungi and might lead to the elaboration of compounds superior to those which we already possess.

Two different methods were carried out—one which we have termed the fungistatic test, and the other a fungicidal test. In the former, cultures of certain fungi were planted on mediums containing various strengths of the medicaments to be tested; the results indicated the *restraining* or *inhibitory* power of the compounds. In the fungicidal tests, the strength or amounts of various medicaments necessary to *kill* cultures was determined. The character of this latter test meets more closely the conditions which are present in human infections, as each case of ringworm or favus represents a culture on or in the skin or its appendages.

We have tested twenty-one chemical compounds or drugs and nine dyestuffs. The compounds investigated were iodin, iodoform, phenol, betanaphthol, mercuric chlorid, sodium oxymercury orthonitrophenolate (mercurophen), ammoniated mercury, mercuric salicylate, calomel, salicylic acid, sodium salicylate, benzoic acid, sodium benzoate, resorcin, sulphur, sodium thiosulphate (hyposulphite), sodium hydroxid, chrysarobin, neorobin, arsphenamin and neo-arsphenamin.

In the fungistatic test, three parasites were employed, two types of ringworm fungus, *Trichophyton rosaceum* and *Microsporon audouini*, and *Achorion schoenleinii*, the parasite of favus.

TECHNIC OF FUNGISTATIC TESTS

In these experiments, our purpose was to determine approximately the highest dilutions of various dyes and medicaments incorporated in a solid culture medium capable of inhibiting the growth of three pathogenic molds: *Trichophyton rosaceum, Microsporon audouini, Achorion schoenleinii.*

With the exception of crystal violet, all of the dyes were prepared by Grübler. Each dye and medicament was prepared in a 1 : 100 solution or suspension in sterile distilled water, and higher dilutions were prepared in series of sterile test tubes in amounts of 1 c.c. Numerous controls were included in each set in which sterile water was placed.

To each tube was added 4 c.c. of Sabouraud's maltose medium titrated to 1 per cent. acid to phenolphthalein, melted and cooled to 40 C. The agar and solution or suspension of dye or medicament

were mixed, slanted, and allowed to harden. These tubes were then seeded with the respective cultures. As a general rule, each dye and medicament was tested in twenty-four dilutions with each of the three cultures; and each experiment was repeated twice, and the majority three times, in order properly to check the results. After seeding, the tubes were kept at room temperature. The results were read at weekly intervals, but those given in the tables represent the final readings made on the sixth to eighth week of each experiment.

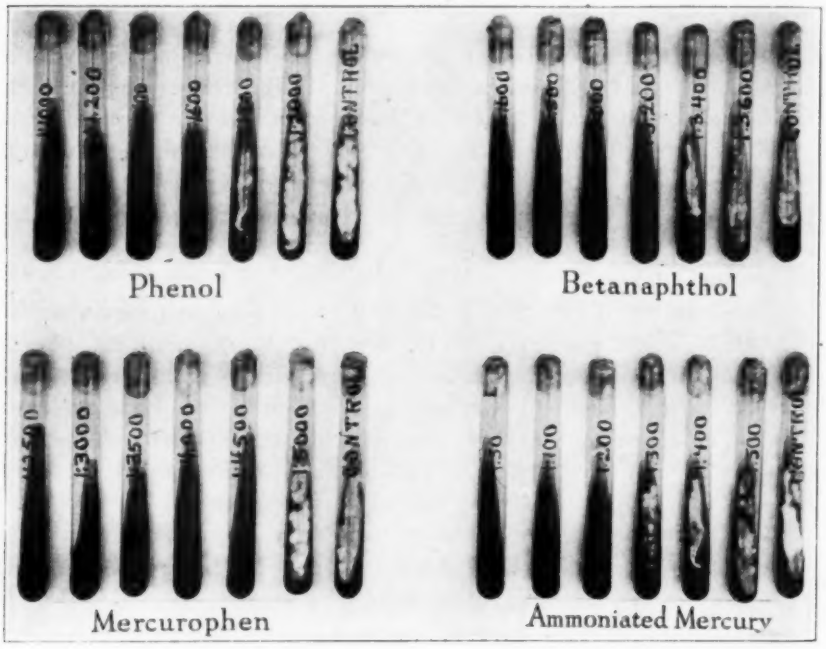

Fig. 1.—Fungistatic test, showing restraining inhibiting influence of various medicaments and stains on Trichophyton rosaceum.

As is true of bacteriostatic (antiseptic) tests, the highest values are found during the first week or ten days in these experiments; but during prolonged incubation the restraining activities of the higher dilutions of the substances being tested are lost until a period is reached when the results remain stationary, thus disclosing the fungistatic activity.

Table 1 gives the restraining power of the different drugs against these three fungi. It will be observed that against *Trichophyton rosaceum,* iodin exerted an infinitely greater inhibition than any other compound; next in order, but far behind, came mercurophen, mercuric chlorid and betanaphthol.

Against the *Microsporon audouini,* mercurophen stood first, closely followed by iodin, with mercuric chlorid and betanaphthol next. With *Achorion schoenleinii* as the test parasite, mercurophen exhibited a marked superiority over iodin, which came second, with mercuric chlorid third.

Reading down the list, one is somewhat astonished to note the low inhibiting power of certain medicaments which have acquired reputations as remedies of value against ringworm. Reference will be made later to this observation.

TABLE 1.—The Fungistatic Activity of Various Medicaments

Medicament	Highest Fungistatic Dilutions for		
	T. rosaceum	M. audouini	A. schöenleinii
Iodin	1:100,000*	1:10,000†	1:15,000‡
Iodoform	1:400	1:400	1:300
Phenol	1:1600	1:1600	1:1200
Betanaphthol	1:3200	1:3000	1:1000
Mercurophen	1:4500	1:12.000	1:47,000
Mercuric chlorid	1:4000	1:5000	1:6000
Ammoniated mercury	1:200	1:300	1:1600
Mercuric salicylate	1:200	1:600	1:800
Mild mercurous chlorid	1:100	1:400	1:300
Salicylic acid	1:50	1:100	1:150
Sodium salicylate	Not in 1:20	1:25	1:200
Benzoic acid	1:40	1:200	1:200
Sodium benzoate	1:20	1:25	1:25
Resorcin	1:200	1:300	1:1600
Precipitated sulphur	Not in 1:10	Not in 1:10	Not in 1:10
Sodium thiosulphate	Not in 1:20	1:300	1:300
Sodium hydroxid	1:1000	1:750	1:3000
Chrysarobin	Not in 1:10	Not in 1:10	Not in 1:10
Neorobin	Not in 1:10	Not in 1:10	1:10
Arsphenamin (acid solution)	1:100	1:160	1:400
Arsphenamin (alkaline solution)	1:50	1:150	1:200
Neo-arsphenamin	1:20	1:100	1:75

* 1:2000 of a 2 per cent. solution (2 gm. iodin crystals; 5 gm. potassium iodid and 100 c.c. water) = 1:100,000 of pure iodin.
† 1:200 of a 2 per cent. solution = 1:10,000 of pure iodin.
‡ 1:300 of a 2 per cent. solution = 1:15,000 of pure iodin.

Studies of the fungistatic power of various dyestuffs are shown in Table 2. It is here seen that brilliant green decisively transcends all the other laboratory stains in restraining the growth of molds. Only against the parasite of favus is it equaled by crystal violet. All of the remaining dyes are infinitely inferior.

TABLE 2.—The Fungistatic Activity of Dyes

Dyes	Highest Fungistatic Dilutions for		
	T. rosaceum	M. audouini	A. schöenleinii
Brilliant green	1:16,000	>1:47,000	<1:2500
Crystal violet	1:500	1:6000	<1:2500
Methylene blue	1:200	1:300	1:800
Methyl green	1:200	1:800	1:600
Gentian violet	1:200	1:200	1:150
Fuchsin	1:200	1:100	1:20
Eosin	1:20	1:10	1:100
Safranin	Not in 1:200	1:200	1:600
Bismarck brown	1:200	1:150	1:100

TECHNIC OF FUNGICIDAL TESTS

As has already been intimated, more importance is to be attached to the fungicidal tests, because these denote the comparative destructive influence of medicaments on the growths of fungi.

In these experiments, our purpose was to determine approximately the highest dilutions of various dyes and medicaments capable of killing the cultures of the fungi, employed in fifteen minutes, one hour, three hours and twenty-four hours.

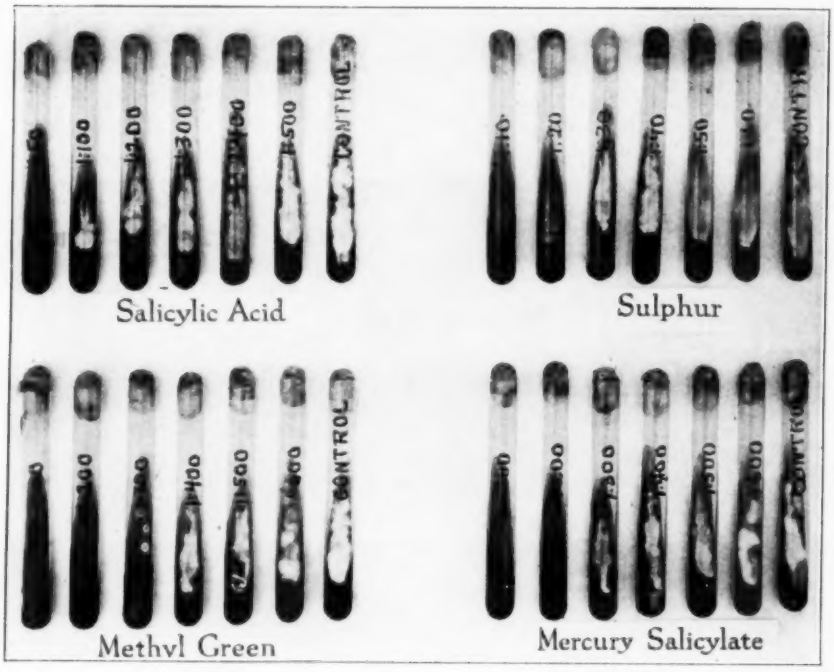

Fig. 2.—Fungistatic test, showing the restraining or inhibiting influence of various medicaments and stains on Trichophyton rosaceum.

Cultures of the respective fungi were removed from Sabouraud's maltose medium with sterile saline solution and shaken mechanically with glass beads for several hours, until a homogeneous suspension was secured corresponding in density to Tube 5 of the McFarland nephelometer.

Solutions of the dyes and medicaments were prepared with distilled water. Equal parts (0.5 c.c.) of varying dilutions and suspension of culture were mixed and kept at 20 C. At intervals of fifteen minutes, one hour, three and twenty-four hours, a portion of each mixture was cultured by transferring several loopfuls to slants of Sabouraud's maltose medium. Controls were included in each experiment in which

sterile saline solution was employed. These cultures were kept at room temperature for from three to four weeks, and the results read. These are recorded in Tables 3, 4 and 5.

One would expect that stronger concentration of the compounds would be necessary to kill fungi than to prevent their growth; the investigations prove this assumption to be correct. In the fungicidal tests, brilliant green falls from its high estate and is supplanted by crystal violet. All of the dyestuffs, however, are markedly inferior to the other medicaments.

TABLE 3.—FUNGICIDAL ACTIVITY FOR TRICHOPHYTON ROSACEUM

	Exposure			
	15 Minutes	1 Hour	3 Hours	24 Hours
Brilliant green	1:25	1:80	1:200	1:200
Crystal violet	1:25	1:50	1:50	1:200
Gentian violet	Not in 1:25	1:25	1:50	1:50
Iodin	1:5000*	1:5000	1:7500†	1:10 000‡
Phenol	1:25	1:25	1:50	1:150
Betanaphthol	1:25	1:25	1:50	1:100
Mercuric chlorid	1:10,000	1:10,000	1:10,000	1:15,000
Mercurophen	1:10,000	1:10,000	1:10,000	1:15 000
Sodium hydroxid	Not in 1:15	1:15	1:25	1:25

* 1:100 of a 2 per cent. solution.
† 1:150 of a 2 per cent. solution.
‡ 1:200 of a 2 per cent. solution.

Against *trichophyton rosaceum,* mercurophen is slightly superior to mercuric chlorid, with iodin third. Phenol and betanaphthol are far inferior. The same sequence holds true for *Microsporon audouinii* and for the parasite of favus (*A. schoenleinii*).

TABLE 4.—FUNGICIDAL ACTIVITY FOR MICROSPORON AUDOUINI

	Exposure			
	15 Minutes	1 Hour	3 Hours	24 Hours
Brilliant green	1:100	1:200	1:500	1:500
Crystal violet	1:1600	1:1000	1:2000	1:5000
Gentian violet	1:25	1:50	1:100	1:200
Iodin	1:500	1:1000	1:2000	1:5000
Phenol	1:100	1:100	1:100	1:200
Betanaphthol	1:50	1:50	1:100	1:100
Mercuric chlorid	1:2000	1:5000	1:10,000	1:15,000
Mercurophen	1:5000	1:10,000	1:10,000	1:20,000
Sodium hydroxid	Not in 1:25	Not in 1:25	Not in 1:25	Not in 1:25

BACTERICIDAL ACTIVITY OF COMPOUNDS TESTED

Five of the most favorable compounds, mercurophen, mercuric chlorid, crystal violet, iodin and brilliant green, were tested for their destructive power on *Staphylococcus albus.* Their sequence here indicates the order of their efficacy.

It is here observed that while the mercurials come first, crystal violet has a stronger bactericidal effect than iodin, which has been much used as a skin disinfectant in surgery. It should be noted, however, that the iodin in these tests was used in aqueous solution in order to avoid confusion of interpretation from the effect of alcohol. The tincture of iodin might well be more germicidal as such, and moreover the alcohol would doubtless facilitate penetration into the upper layers of the skin.

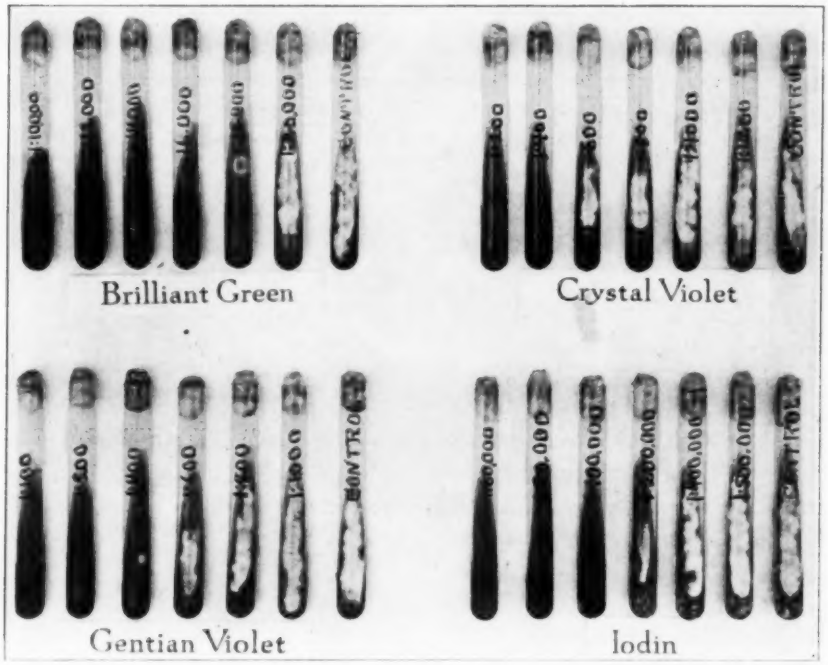

Fig. 3.—Fungistatic test, showing the restraining or inhibiting influence of various medicaments and stains on Trichophyton rosaceum.

The superiority of crystal violet over other stains in killing the staphylococcus is of interest in connection with the studies of Farley[1] on gentian violet. Farley incorporated gentian violet in maltose agar for the purpose of restraining the growth of gram-positive bacteria and thus aiding the isolation in pure culture of molds from the skin and hair. He found that 1 : 500,000 dilution would restrain the growth of those bacteria; while 1 : 250,000 did not inhibit the growth of molds.

1. Farley, D. L.: The Use of Gentian Violet as a Restrainer in the Isolation of Pathogenic Molds, Arch. Dermat. & Syph. **2**:459 (Oct.) 1920.

Our investigations indicate that very much stronger concentrations could be used without inhibiting mold growth.[2]

PRACTICAL APPLICATION OF RESULTS

One is somewhat astonished at the relatively poor showing in inhibiting the growth of molds exhibited by salicylic and benzoic acid. These are the essential ingredients in Whitfield's ointment, the favorable effect of which in the treatment of chronic ringworm of the cutaneous surface appears to have strong clinical support.

TABLE 5.—FUNGICIDAL ACTIVITY FOR ACHORION SCHOENLEINII

	Exposure			
	15 Minutes	1 Hour	3 Hours	24 Hours
Brilliant green	1:100	1:100	1:500	1:500
Crystal violet	1:1000	1:1000	1:1000	1:3000
Gentian violet	1:25	1:50	1:100	1:150
Iodin	1:2000	1:4000	1:5000	1:5000
Phenol	1:100	1:100	1:200	1:500
Betanaphthol	1:50	1:50	1:50	1:100
Mercuric chlorid	1:2000	1:5000	1:10,000	1:15,000
Mercurophen	1:2000	1:5000	1:15,000	1:20,000
Sodium hydroxid	1:25	1:100	1:1000	1:1000

TABLE 6.—BACTERICIDAL ACTIVITY FOR STAPHYLOCOCCUS ALBUS

	Exposure			
	15 Minutes	1 Hour	3 Hours	24 Hours
Brilliant green	1:500	1:500	1:600	1:800
Crystal violet	1:1000	1:1000	1:1500	1:3000
Iodin	1:100	1:100	1:100	1:200
Mercuric chlorid	1:1600	1:1600	1:1800	1:3200
Mercurophen	1:1600	1:2000	1:2000	1:4000

It is possible that the beneficial effects of this ointment may be due to the exfoliative effect of salicylic acid rather than to its fungicidal influence.

The laboratory studies herewith reported cannot subvert, and are not designed to controvert, established clinical judgments. They are merely test tube experiments, which must be subjected in due course to clinical trial. They may be regarded as establishing leads to clinical experimentation. The ultimate results may be disappointing, or they may be gratifying. It may, furthermore, prove desirable to subject the most favorable compounds to chemical alteration with the view of enhancing their value. We have had a brief but favorable experience

2. We would suggest that crystal violet be used instead of gentian violet, as crystal violet is a pure substance, whereas gentian violet is an impure compound of variable composition containing crystal violet, methyl violet and perhaps other substances.

with one compound in the treatment of tinea cruris; but the number of cases treated is not sufficiently extensive to warrant a definite statement at this time.

CONCLUSIONS

1. We have endeavored by a fungistatic (restraining) test and a fungicidal (killing) test to determine the affinities of various commonly employed medicaments and of certain laboratory stains for three different pathogenic molds.

2. We have found selective affinities of certain of the medicaments and dyes for the molds as well as for bacteria.

3. At the present time, the use of these tests appears to be an aid in the isolation of molds and bacteria in pure culture.

4. Iodin transcends all other medicaments in restraining the growth of certain molds, but in aqueous solution it is inferior to certain other drugs in killing them.

5. Sodium oxymercury orthonitrophenolate (mercurophen) is superior as a fungicide, in the test tube, to mercuric chlorid and to iodin, and far superior to the other medicaments tested.

6. Among the dyestuffs, brilliant green was the best restrainer of growth, but crystal violet proved distinctly superior as a fungicide. All of the dyes, however, were inferior to the mercurial preparations.

7. These experiments should not be interpreted in such a manner as to subvert established clinical judgments. The findings, however, should stimulate clinical experimentation.

DISCUSSION

DR. CHARLES M. WILLIAMS, New York: We are very much indebted to Dr. Schamberg for this work on the germicidal action of drugs in the skin and for the conservatism with which he has interpreted the results. We shall be thankful to find a reliable drug. It seems that neither benzoic acid nor salicylic acid has any effect on mycotic organisms; and yet there is no question that mild cases are cured by applications of Whitfield's ointment. The exfoliation is probably the most important factor. I think the irritation is a very good thing. This means increased blood supply and a greater power of bringing about a resistance to the organism itself, as we know that kerion is cured by the very acuteness of its own inflammatory reaction.

The work with iodin was interesting; but in practice I have found that iodin is not so useful as we would expect. The boy I mentioned as having tinea on the toes had been applying iodin for some weeks, and I never found more organisms than in that case. There is no way that we can account for the cure by salicylate or benzoic acid, or the roentgen ray, except by their influencing the reaction of the patient.

DR. HARVEY P. TOWLE, Boston: The important thing in Dr. Schamberg's paper, it seems to me, is that, whereas we have been relying on one drug for the cure of all fungus diseases, it is here illustrated that we must select the one that has the most effect on the various types as shown by laboratory experiments.

That is well illustrated in his tables, which I think, bear out our clinical results. Unquestionably, the laboratory conclusions will be modified greatly, because we are dealing, in the clinic, with living tissue; whereas, Dr. Schamberg, as he pointed out, is dealing, in the laboratory, with the inert substances. That is a tremendous factor; but if we learn to pick out a given remedy in a given case with a direct etiologic factor, we shall have made great advance.

Dr. Samuel E. Sweitzer, Minneapolis: I should like to ask what diluent Dr. Schamberg used, particularly in iodin. It is possible that, if alcohol was used, it might have had some effect. I should also like to ask if, in his future studies, he will take up the question of potassium permanganate. This will frequently bring about a rapid disappearance of the vesicles.

Dr. Walter J. Highman, New York: In 1908, Professor Jadassohn set me to work on a task similar to the research Dr. Schamberg and his co-workers have undertaken less crudely. One of the things he was anxious to determine was whether the vehicles in which parasiticides were used affected their activity. It was brought out that aqueous and alcoholic solutions were more effective; that the incorporation of any medicament in oil or cream diminished its effect two to five fold. In Dr. Schamberg's work, so far as the clinical domain is concerned, it will be necessary, I think, to take into consideration the effect on the parasite of the excipient that is employed in using the medicament clinically. This is only a practical point, perhaps, but it will have to receive consideration.

For the rest, I was amazed at the mathematical accuracy with which the various strains of organisms employed by Dr. Schamberg responded or did not respond to the various medicaments tested, and it is gratifying to see this particular branch of parasitology removed from the field which Sabouraud so long ago exhausted.

Dr. Harry E. Alderson, San Francisco: I should like to ask Dr. Schamberg about the effect of some of these drugs applied in powders. I have recently had the pharmacist make up some crayons containing salicylic acid and benzoic acid with starch and magnesium carbonate. I have used these in a few cases of tinea cruris with good effect. These crayons are not so hard that they irritate the skin and not so soft that they crumble; but they leave an adhesive powder on the skin without much rubbing being necessary.

Dr. William Allen Pusey, Chicago: I am obliged to Dr. Schamberg for these definite facts and am willing to let their application take care of themselves. I think this would be borne in mind. We are not looking for the interpretation, but first for facts. I think Dr. Schamberg has used to excellent advantage the opportunities he has for such investigation, and I sincerely hope he will give us more reports of the same sort. This is a stimulating appetizer, but not a full meal, and we shall expect more.

Dr. Jay Frank Schamberg, Philadelphia: I think the members have fully understood that this paper is more or less a preliminary communication and merely a report of laboratory data. It gives us certain leads for clinical experimentation and for further work.

In reply to the query as to whether iodin was used in alcoholic solution, I would answer in the negative. It was used in an aqueous menstruum. I have no doubt that alcohol would penetrate more readily; but we wished to avoid complications in formulating our deductions. If you have a thickened skin in which the fungus is embedded, it is necessary to reach the fungus before you can kill it. As Dr. Highman has stated, the incorporation of medicaments in unguents would doubtless lessen their effect.

Whether powders will be more effective remains for investigation; we have felt that the experimental work done will give us certain lines of approach.

After all, we must be careful not to interpret laboratory data too sweepingly in their application to clinical ends, because results in vitro are commonly very different from results in vivo. We will have to follow our test tube results with experimental work on the animal infected with the parasites in question in order to demonstrate their practical value. Mercuric chlorid, while it shows up very well in these tables, even in a solution of 1: 10,000, tends to necrotize tissue cells; so it may be that another drug which we have used will be more advantageous because it does not work material harm on living tissue, but confines its action more to the bacteria.

INOCULATION, AUTOINOCULATION AND COMPLEMENT FIXATION TESTS IN POMPHOLYX (TILBURY FOX) *

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PHILADELPHIA

In 1919, Darier[1] published an article on the vesicular and the vesicopustular eruptions on the hands and feet. In this article, he found mycelia, on microscopic examination, in the majority of those conditions corresponding to the classic description of pompholyx. His conclusions were that, after excluding eruptions of dermatitides due to plants, trauma, trades and the streptostaphylococci (dematitis venenata; dermatitis traumatica; occupational dermatitis, and infectious eczematoid dermatitis), most cases of pompholyx (80 per cent.) were of mycotic nature.

The opinion expressed by Darier in 1919 created widespread interest. This opinion has not, however, been generally accepted up to the present time by independent observers, because of the general failure to demonstrate mold fungi in the typical lesions of pompholyx. As a matter of fact, Darier, in a most recent expression of opinion,[2] stated that he found parasitic mycelia in 80 per cent. of those cases presenting the clinical aspect of pompholyx. This latter opinion places the question in a totally different light; one in which many dermatologists concur.

Sabouraud,[3] whose work with the ringworm fungi is well known, is of the opinion that pompholyx is not of mycotic origin, though there are pompholyx-like lesions that are; that labeling a disease as of mycotic origin because of the microscopic findings alone is insufficient, for the reason that occasional fragments of mycelium of the penicilium may be found living as saprophytes on the skin; thirdly, that cultures are necessary as additional evidence. In a previous communication,[4] we amply confirmed Sabouraud's contentions that the higher fungi,

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* From the Dermatological Research Institute.

1. Darier, J.: Lancet **2**:578 (Sept. 27) 1919.
2. Darier, J.: Presse méd., July, 1922, No. 52, p. 560.
3. Sabouraud: Bull. Soc. franç. de dermat. et syph., 1921, No. 9, p. 441.
4. Greenbaum, S. S., and Klauder, J. V.: Yeast Infections of the Skin, Arch. Dermat. & Syph. **5**:332-344 (March) 1922.

aside from the fission and the budding fungi, may be found on the normal skin, but that under certain conditions they may develop pathogenic properties.

Koch's laws are too well-known to necessitate description here, but they have not as yet been fulfilled in a way to place pompholyx definitely with the mycoses. Darier's studies were entirely microscopic and positive; Sabouraud's studies were both microscopic and cultural, but entirely negative. Sabouraud's studies have been confirmed, not only be me, but by many others. With the opinions of these two eminent dermatologists diametrically opposed, it was thought that perhaps the problem could be approached from other angles; namely, inoculation, autoinoculation and serologic studies.

The importance of having a clear understanding of the condition under discussion cannot be exaggerated, since all dermatologists are not in accord in considering pompholyx a clinical entity. As a matter of fact, it is not always easy to say that such and such a condition of the hands, feet or both is, for example, a trade dermatitis, a streptococcic dermatitis or a dermatitis venenata. All of us are well aware of the fact that more than one factor (bacterium, exotoxin, endotoxin) may lie behind the development of lesions clinically exactly alike. The reason for this is not far to seek, since we know that the skin can react to any irritant in but a few ways; whereas the number of irritants are far more numerous. If the important fact is recognized that clinical lesions with a varied etiology may not differ, it then becomes evident that other means besides clinical, bacteriologic and cultural measures are necessary to differentiate these etiologic factors.

TYPE OF CASE STUDIED

For the sake of clearness, a brief description of the type of case selected for this study follows:

True pompholyx (cheiropompholyx of Hutchinson, dyshidrosis of Tilbury Fox) is characterized by the development of vesicles and bullae on the hands and feet and, notably, the palms, lateral surfaces of the fingers and soles. This acute, generally symmetrical inflammatory disease is further characterized by the development of its manifestations in crops, its tendency to recur and, as regards a single attack, its limited duration. The vesicles, at first small and deep-seated, increase in size, may and often do become purulent, coalesce and later undergo resorption. As a rule, spontaneous rupture does not occur, but accidental rupture of the larger ones is usual. It is to be remembered that all grades of the affection occur, from a few superficial or deep lesions to those involving the entire palm, dorsum of hands and the soles. In order to be absolutely certain that we were dealing with the affection under consideration, only those cases

in which the diagnosis was certain, with well-marked lesions and a history of previous attacks, were included in this study. Abortive cases, such as those in which there were but a few vesicles on the lateral surfaces of the fingers, were not included. The cases selected for this study came from private practice, from the Polyclinic Hospital dispensary of Dr. Jay F. Schamberg and from my own dispensary at the Mount Sinai Hospital.

INOCULATION TESTS

The surfaces of vesicles with clear contents were swabbed with alcohol and punctured with a capillary pipet. Sufficient fluid for the tests was thus obtained, and kept in sterile test tubes. The greater vulnerability of children to ringworm infection was recognized and volunteers were consequently used for the experiments. In control experiments, volunteers whom I had previously inoculated with trichophytons and microsporons, from their own scalp lesions, and with cultures from the laboratory, generally developed ringworm of the parts inoculated (glabrous skin) within from seven to ten days. It might be here noted that this autoinoculation test in ringworm of the scalp is quite simple and of value not only as an aid to the diagnosis of tinea capitis, but also as a method of determining the presence or absence of cure. The diagnostic lesion is easily eradicated. The volunteers used for the experiments in this study (five in number) were inoculated with a mixture of fluids obtained from different cases of pompholyx and were kept under observation three weeks.

The tests were uniformly negative.

AUTOINOCULATION TESTS

All the patients used for the complement fixation tests underwent an autoinoculation test. The vesicles generally selected were those in which the contents had not become purulent. When this was not possible, purulent contents were used. The surface was swabbed with alcohol, the vesicle punctured with a sterile capillary pipet and the material thus obtained rubbed into a superficially scarified area on the skin, over the deltoid muscle and in the inguinal region, the site of predilection of the epidermophyton. All the tests, following a three-week period of observation, were negative.

COMPLEMENT FIXATION STUDIES [5]

Kolmer [6] showed that, with a polyvalent antigen of *Microsporon audouini*, complement fixation occurred in 78 per cent. of persons suffer-

5. The complement fixation tests were performed by Miss Anna Rule, following the new standardized technic of Dr. John A. Kolmer.

6. Kolmer, J. A., and Strickler, Albert: Complement Fixation in Parasitic Skin Diseases, J. A. M. A. **44**:800-804 (March 6) 1915.

ing with ringworm of the scalp and that the antigens, not only of the microspora but of an achorion as well, were specific in that they did not fix complement with the serums of syphilitic patients or patients suffering with scabies, acne vulgaris, eczema and impetigo. That study seems to indicate that in superficial ringworm infection there is a concomitant development of "ringworm reagin." It was felt, therefore, that if pompholyx is really of ringworm origin, the depth of the lesions would presumably be associated with the development of complement fixing bodies in the blood.

As a result of certain recent studies in the immunologic relationships of the ringworm fungi,[7] it was determined that the fungi, in certain instances, were so closely related that an antigen of some of them was of sufficient value to determine the presence of ringworm reagin produced in rabbits by the injection of many of the others. In the complement fixation tests in this study (twenty subjects), several such antigens were used independently. The antigens used were made from cultures of *Tricophyton niveum-radians, Tricophyton violaceum* and *Achorion gypseum*. Complement remained unfixed in every case tested.

CONCLUSIONS

1. Pompholyx is a clinical entity whose cause remains unknown. When well defined, ringworm as the etiologic factor can be clinically excluded.

2. There are poorly defined or aborted cases of pompholyx whose differentiation from the pompholyx-like lesions of ringworm require microscopic and cultural examinations. Autoinoculation, as a diagnostic test, is of value, but great care in the collection of the material to be used is advised, as severe scarring from secondary coccic infection may occur.

3. There are pompholyx-like eruptions having a mycotic origin.

1714 Pine Street.

7. Paper to appear shortly.

A CONTRIBUTION TO THE TREATMENT OF PHYTOSIS OF THE FEET*

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ATLANTA, GA.

As the term epidermophytosis seemed about to supplant the ancient titles (White, the author, and others), workers demonstrated that the tricophytons are the majority of the offenders, with others of the higher fungi (Wende-Collins) capable of producing disease. The term tinea, defined worm, was employed as far back as 1829 and has continued to cover several different dermatologic conditions. Tricophytosis, for years, and epidermophytosis, of late, bade fair to break the reign of tinea, but now we must coin a new name. Taenia means tapeworm; tinea, any worm.

While investigators seem not to have complied with Koch's law, the presence of these fungi, with resistance and recurrence of disease induced, as well as the usual sources and methods of infection, leaves little doubt of their pathogenicity. As to the distribution of this class of disease, it is at least universal, almost pandemic, among men; and for the simplest of reasons. Casual reference to "toe trouble" or "foot trouble" in conversation anywhere is more than likely to arouse interest, though it is a natural condition. Cases in children as young as 7 are in my records, an evidence of parental carelessness. I have never seen a very old person with the disease. There is a Y. M. C. A. building here, the shower baths of which are open to all members, whether resident or not. Even before the war, this disease was prevalent. During the war, lay over soldiers often used these baths. The disease has been so common of late that I have heard it referred to as the "M. A. disease." Public baths and showers, the more menacing, even golf club showers, are the leading sources of infection. Socks and stockings may actually bring the disease from the laundry, or reinfect the owner if, as Mitchell suggests, the organisms survive laundering.[1] There is some evidence to support the belief that the

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*A clinical paper, based on private cases.

1. Many housewives wash socks and stockings at home without boiling. Washerwomen do not boil them. The head of a large laundry states that these articles, of the same colors, are put in meshed bags and run through the mangle, with little heat, the cleansing chemical probably being sodium carbonate. They are then placed on hollow, metal forms, steam-heated to 180 or 200 F., the drying process requiring from two and one-half to four minutes. I am now instructing patients to have hosiery boiled at home for at least fifteen minutes.

fungi may be water-borne, as in a case supposedly contracted from a Georgia stream and another through a laceration of the bare sole of a young woman at a bathing beach near Detroit, though the latter infection could have come from a preceding infection of the foot. The family tub and towels, and the exchanging of footwear, provide other sources of infection.

The disease, while easily transinoculated by the patients' hands, or auto-inoculable, is very rarely directly contagious. A curious illustration of variations in personal local immunity is the frequency of involvement of one foot alone, this condition often persisting for months, even indefinitely. Such local persistence with frequent recurrences is also strong evidence of dormancy and periodic growth of retained organisms, rather than of positive reinfection in loco.

These fungi are known to have survived from five to nine months in a dry envelop, but the ultimate longevity of some of them is yet to be determined. They may rival the Egyptian wheat which germinated after reposing for 2,000 years in a tomb. Mitchell has shown viability of certain phyton forms after boiling in potassium hydroxid solution.

That the organisms may lie dormant during cool or cold weather, either in contaminated articles of apparel or actually in the epidermis, in spite of normal desquamation, is well established. Recurrence of disease in practically the same areas occupied during the preceding summer and the depth from which lesions may arise, as on the plantar surfaces, at least favors the probability of epidermal hibernation. Even in Atlanta, where we average less than one freeze a week in winter and the temperature may get up to 60 F. or higher, many cases give no trouble but reappear as the average daytime temperature reaches 70 F. I see very few of the phytoses in winter, but very many in summer. Yet there are cases even in Boston and Detroit that are unchecked by cold weather, and they are also seen in Atlanta.

Whether being in heated homes, cars and offices, with a minimum of exposure to cold, or whether the variety of organism is responsible for these exceptions, we have no positive knowledge. That warmth and moisture, not necessarily hyperhidrosis, do encourage growth of these fungi is known. In this connection, it is a curious fact that we rarely see phytic infection of the feet in cases of bromidroses.

The depth to which the phytons penetrate, as in plantar regions and the fourth interspace, as well as in callosities, constitutes the primary reason for persistent recurrences and difficulty of cure. Extracorporeal destruction of germs or fungi and destruction in vivo are vastly different propositions. Dry air and sunlight may kill tubercle bacilli, drying suppress gonococci, soap destroy *Spirochetae pallidae* and radiation disintegrate cancer cells, but for cure every organism or

cell must yield. When contact is established, as in vitro, such accomplishment may be easy. In the tissues, we must get at the cause or depend on the natural resistant forces of the body cells, reinforced if possible. Schamberg's weak iodin destroys the fungi in vitro, and tincture of iodin is practically useless as applied by patients to these foot conditions. Ruggles' tincture of iodin 1, spirits of camphor 7, did well until his patient went on a six weeks' vacation and left off treatment, with the usual relapse.

Ripened or developed lesions yield rather readily to almost any good dermatologic treatment, most of which are more or less germicidal, though not by far so rapidly as a simple dermatitis. Hidden organisms delay recovery, just as they, with now and then a reinfection, prevent permanent cure. After getting relief, the majority of patients disappear.

TREATMENT

In order to effect a cure, it is imperative that we rid the patient of all harbored fungi, and, in doing this, endeavor to adapt remedies to the destruction of organisms present in articles worn. Whitfield's principles of treatment must be followed in one particular at least, and to extremes. These cases require constant desquamating and exfoliating; in other words, persistent and intensive peeling. This is best accomplished with salicylic acid, combinations of methods to be mentioned later activating its effect. Benzoic acid is probably almost inert as a fungicide, as shown by Schamberg.

Pus cases, secondary coccic infections, have needed but a single remedy to clear them up in from twenty-four to forty-eight hours, whether there be a few pustules or the greater part of the plantar surface is undermined. Small lesions are broken up and the larger buttonholed in such manner as to prevent reclosure and yet leave sufficient epidermis for protection of tender surfaces until new can form. The official ointment of ammoniated mercury, in half or full strength, is specific. A few pus conditions may be too inflammatory, or, more likely, the lesions may have been stained with tincture of iodin, the latter condition contraindicating mercury. A mild boric ointment is satisfactory as a beginning in these cases.

Ointments are heavily applied, with cotton to retain them, and changed at least twice in twenty-four hours. Because of their messiness, doubtful utility and injury to footwear, I do not employ ointments in the nonpyodermic cases, save at night in conditions tending to become very dry.

Stains and dyes have been avoided because of their character as well as doubt of their ability to reach or affect the phytons. Treatment has been limited largely to powders and to mechanical procedures.

It may be stated with positiveness that the majority of cases of phytosis must be treated after the war cry of the Tank Corps, very few yielding definite results under gentle management. Soap, water and scrubbing (Williams) must be employed, not only for cleanliness but also to get rid of as much dead epithelium and as many fungi as possible. Vesicles are broken up, bullae and large subepidermic lakes torn to pieces or buttonholed, as in the pus conditions, and shreds are cut or peeled away in all cases. Plantar callosities are cleansed with soap and water or gasoline and covered with salicylic acid, roofed over with narrow overlapping strips of adhesive plaster—wide sections do not fit—and this dressing renewed as often as it loosens. As the seminecrosed, broken-up, rubber-like epidermis begins to separate, it is removed. The salicylic acid may also be employed on interspace accumulations, particularly the wide fourth. At the same time, salicylic acid is used in all powders, 1:8, or stronger, often alone, on the feet and in socks.

The gamut has been run with everything from a little boric acid even through ground-up hexamethylenamin and, occasionally, thymol iodid or calomel, to sulphur. Salicylic acid in the socks produces definite exfoliation of thick epidermis, as of plantar surfaces, and desquamation alone of lateral and dorsal areas, partly through greater contact from drifting down in the former instance, but also because the thickened epidermis is farther from its blood supply, and so less vital. It not only opens their lair, but possibly has some destructive action on the organisms; spores, as always, being perhaps the hardest to kill.

Proof that going into the treatment of the phytoses is entering a maze in which we wander rather vainly seeking a definite objective exists in the many remedies tried and abandoned or employed with scant success.

If formaldehyd vapor from an open bottle in the laboratory "killed all the ringworm cultures," why could the liquid or vapor not act in phytosis? Vapor was used under a rubber cap, in scalp cases. The disease required its usual time for cure. There is no practical way of applying vapor to foot cases, and any percentage of the liquid is too irritating and of slight penetration.

Hexamethylenamin grossly pulverized was put in socks, shoes and slippers, with the hope of getting some free formaldehyd. The soles were tanned and thickened, but vesicles and small bullae continued to appear even in the leathery tissue. Leather insoles were ruined by the drug. Benzin, or gasoline, applied to perfect sheaths of little black bugs on new shoots of grapevines killed both the bugs and a foot or two of new vine. Applied to broken vesicular points on the toes, it intensely aggravated the itching. Saturating the socks with it in the hope of sterilizing the feet and foot coverings had no apparent effect.

Surgical solutions were not considered worthy of trial and germicidal ointments, even the pus destructive ointment of ammoniated mercury, has been of doubtful utility in the phytoses. Any effect from the roentgen rays was simply due to cell reaction, and transitory. On several occasions, new erythematovesicular patches were treated by momentary freezing with ethyl chlorid, in the hope that refrigeration might hasten recovery. Carbon dioxid snow would have been cheaper, but the treatment was applied in the patient's room. Results of this brief freezing were uncertain.

In desperation, a physician even applied: Oleate of mercury and olive oil, four parts each, and sulphuric ether, sixty parts (mixed), an instantly effective remedy for pediculosis pubis and their ova. Even this mixture had practically no effect, except to ruin the shoes.

Powder prescriptions have always had talcum as the vehicle, since it is insoluble and keeps dry.

Powders have run from the ancient: salicylic acid and boric acid one part each, pulverized zinc oxid from four to eight parts, and pulverized talcum to make thirty parts (mixed); on through: salicylic acid, from two to four parts, benzoic acid, four parts, and pulverized talcum to make thirty parts (mixed); and salicylic acid, two parts, calomel, four parts, and pulverized talcum to make thirty parts (mixed).

Even pulverized alum has been added to some of these prescriptions for its drying effect; and, finally: salicylic acid and precipitated sulphur, fifteen parts each (mixed).

He rubbed as frequently as possible on the hands of a patient who could treat them but little during the day; applying at night: salicylic acid and precipitated sulphur, four parts of each, and zinc oxid ointment to make thirty parts (mixed), on all affected parts. The patient has done well.

A paste of sulphur and lard hastened recovery in one case Whitfield's ointment, stronger than the original, is still employed in some cases at night, and occasionally, the ammoniated ointment or petrolatum.

It will be seen from the foregoing that salicylic acid is depended on as the sheet anchor in all prescriptions.

There has been no opportunity to evaluate results from soaking the feet at night in hot water, salt water or ice water, or from washing them with gasoline, the majority of patients having been unwilling to fight the disease to a finish.

In the light of later experience, and through study of old case records, I am inclined to believe that pompholyx is not a distinct disease, as we get these exact lesions, "sago-grains" and all, in the phytoses.

REPORT OF CASES

CASE 1.—J. W. C., aged *23*, first seen, May *25*, 1892, had six weeks before developed deep bullae and some excoriations on the left toes and foot. When examined, there were several ulcers, with pus and blood, and anterior plantar, flat bullae and denudations. Much of the pus was green. "Antiseptic" salves and powders were employed, and some "mixed treatment" was given, on a dubious history. The foot was well in fifteen days.

November *2*: Pompholyx which had developed in the sole of left foot as a group of deep vesicles was drying up.

April 6, 1893: The patient had another attack of pompholyx, with deep-seated, shot-like vesicular lesions.

June *2*: New vesicles developed. The patient had been using:

		Gm. or C.c.		
℞	Resorcin	1	4	gr. xx
	Zinc oxid	4		ʒ i
	Pulverized talcum.....q. s. ad	30		ʒ i

July 14: Bullae developed beneath the first and second interspaces of both feet. Asiatic pills were prescribed, and for local application:

		Gm. or C.c.		
℞	Resorcin (pulverized)	1	4	gr. xx
	Salicylic acid	1		gr. xv
	Talcum (pulverized).....ad	30		ʒ i

There was hyperidrosis pedum. The eruption was better in two weeks.

March 7, 1894: A prescription for treating seborrhea of the scalp was given the patient. No complaint was made of the feet.

May 10: On both soles, especially beneath the arches, there were pin-head to nail-head diameter vesicles and bullae, and note was made of the "same old trouble." A 1:60 potassium bichromate solution was ordered as a wash and a bidaily dressing:

		Gm. or C.c.		
℞	Salicylic acid	2		ʒ ss
	Resorcin	2		ʒ ss
	Magnesium carbonate	4		ʒ i
	Olive oil.....q. s.	30		ʒ i

May 12: The old lesions were improved, and there were a few new ones. The patient died within the following year. His was a typical case of phytosis, the summer type.

CASE *2*.—Mrs. H. T., aged *29*, first seen May 8, 1912, had pompholyx of the hands and feet, first noted in the spring of 1910, and again in the spring of the present year. On the palms, the fingers over the nail roots and on the toes, there were vesicles and erythematosquamous sequelae. On the soles and sides of the feet, there were bullae up to quarter of a dollar in size. Lesions were ordered broken up and boric acid and salicylic acid, one part each, zinc oxid (pulverized), eight parts, and talcum (pulverized) to make thirty parts was ordered kept on in white stockings and gloves.

The lesions began to dry, but new and painful flat bullae appeared, and new vesicles on the palms and fingers. Treatment, as for dermatitis or eczema, continued through prolonged dry, scaly and occasional vesicular periods, until August *28* when the affected areas showed but slight redness and scaling. All were healed, September *25*.

May 7, 1921: The patient had had only one or two slight recurrences. At present, a vesicular to thick scaly itchy patch was present on the dorsum of one finger, and a small disk in the right submaxillary area. The latter soon healed, with simple treatment; the finger was resistant. Recurrence on the finger and a patch on one sole developed in September, and treatment was continued, still without recognition of the possibility of phyton infection, and certainly no treatment was given for this condition. The patient, who was hypersensitive, had plant dermatitis meanwhile, the last outbreak, on the forearms and hand, following gathering garden peas, in May, 1922, at which time the old dermatoses had long since disappeared.

CASE 3.—A medical student, from the country, had had trouble with his feet, summer and winter, for more than a year. When first seen, the anterior half of the plantar epidermis of the left foot was undermined with pus, and there was the usual condition of the toes. The pus was rapidly eliminated with ointment of ammoniated mercury. A large callus beneath the anterior arch was gradually removed with salicylic acid and adhesive plaster. Dermatitis of the toes was reduced by the salicylic acid, calomel and talcum powder; but the use of salicylic acid alone for the whole foot and peeling the sole to infantile thinness really accomplished the cure. This case was fought from fall to spring and definitely cured. The feet were always damp, partly for the reason that he wore overshoes in bad weather and kept them on indoors.

CASE 4.—A college professor, seen recently in May, when the daily temperature was running above 80 F., had had the condition for six summers, always affecting the external three toes of the right foot. It was never present in cold weather and had never been conveyed elsewhere, though the patient was most careless in handling the condition. Clinically, it was a perfect type of phytosis.

CASE 5.—This case is biographic of the disease as affecting the feet of a medical man with whom my relations were not exceeded by those of the Beaumont-St. Martin partnership. In 1918, he contracted the condition in quarters at a base hospital. This erythematosquamous dermatitis of lateral surfaces of the toes and interspaces, with fine fissuring of the latter, was attributed to the shower bath which was so strongly chlorinated that it irritated the eyes. The condition disappeared in cold weather.

In 1919, in Atlanta, there was recurrence with the advent of warm weather, vesicles now appearing about the toes. Diagnosis was made and careless stepping on a boarding house bath rug incriminated. All kinds of treatment and experiments were carried out; however, the salicylic and benzoic powders with talc were employed mostly, as well as occasional trials of most unusual procedures. The lesions disappeared by the time of frost, though the patient was rarely and briefly exposed to cold.

1920: The condition reappeared with the steadily warm days, it now involving also the anterior sole, from vesicles to small bullae. The slippers used in army were worn at home winter and summer. Summer socks, the same used even thus far in 1922, and an old pair of canvas shoes were worn during the hot weather, far into the summer of 1921. The disease had always appeared before these shoes were put on and even with new shoes. Slippers, socks and shoes got practically as much treatment as the feet.

1921: The toes had never been as uniformly affected as in the first year or two. Now the vesicles and deep bullae appeared as far back as the midsole, and two or three of the toes were showing small patches of vesicles dorsolaterally, especially near the nails. Vesicles were broken up and salicylic

acid rubbed into all new areas or lesions. Gasoline was tried again in spite of its former bad effect on broken points, the socks being saturated with it and slippers or shoes put on. Later, ethyl chlorid freezing was practiced on all new outbreaks, and this season finished with the salicylic-sulphur-talc powder.

There was never hyperhidrosis, though there was a slight dampness of the socks winter and summer. Salicylic acid beneath adhesive plaster on a new patch caused a violent outbreak of vesicles beneath the plaster, peripherally to the salicylic acid application.

In April, 1922, there were a few days on which the temperature rose above 70 F. My impression is that the same socks, some pairs of which had been worn for several summers, cotton or mercerized, bluish-gray, were resumed about this time. Promptly, a large pea-sized bulla appeared beneath the center of the right heel, and a dime-sized patch of vesicles developed on the inner side of the arch of the same foot. All lesions were broken and rubbed with salicylic acid, sometimes the salicylic-sulphur mixture, and for the following weeks the inside of the socks were heavily dusted with salicylic acid, four parts, precipitated sulphur, eight parts, and talcum (pulverized) to make thirty parts (mixed). There was no night treatment. The bullae never itched but they were painful. There was intense itching of the primarily vesicular patches, just as this year, long after there was nothing but a little redness and scaling. At the end of May, there had been no new lesions; the site of the bulla peeled off, and the little patch was pink, thinly desquamative and a bit itchy. Many days in May and June, 1922, the thermometer rose as high as from 82 to 85 F. and the humidity was excessive. Use of the powder was continued and the left foot, thus far, has escaped and the right foot has shown no further lesions.[2] The sulphur accentuates the peeling effect of the salicylic, much of the latter being synthetic and probably weak locally.

We are not prepared thus early to believe that the final chapter in this biography can be written. The same lot of socks, washed by a colored woman, is being worn; the shoes were new in the winter. There is a pair of oxfords of last summer yet to be tested, though personally I would be satisfied to let well enough alone.[3]

This patient will never step on any bath floor and has the greatest repugnance for shower baths—the cement floors of all of which we believe infected.

SUMMARY AND CONCLUSIONS

It is admitted that the term phytosis, an amputated extremity of more definitely descriptive names, is a makeshift. Epidermophytons appearing now in the minority in the tricophyton group, we cannot properly continue epidermophytosis as descriptive. If the term tinea, used since 1829, means worm, it is as bad as many other misnomers. As it is impossible to make a laboratory diagnosis in every case, we must employ the loose term phytosis as a convenient designation.

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2. The oxfords were later worn through a period of hot June weather, the temperature going as high as 93 F. The powder was never omitted.

3. Post seu propter hoc, within forty-eight hours after putting on a pair of socks not worn since last summer a single pruritic vesicle appeared above the outer edge of right heel. Severe treatment produced terminal peeling on the fifth day.

This disease group has few if any individually distinctive clinical features pointing to the type of fungus, even as the multitude of dermatitides venenatae may result from as many kinds of irritant as there are cases.

The disease is less contagious than infectious through an intermediary, as witness the frequency of unilateral cases and common sources of acquirement. Cases reported from practically every part of the world almost demonstrate pandemicity.

Commonest foci of infection are public baths, especially showers, and family contamination of rugs and floors and perhaps towels. Reinfection occurs from shoes, slippers and socks, even after laundering, or from laundry transference. The duration of viability of the fungi is from many months to an indefinite period, even in dry air. The majority of cases seems to indicate cold weather dormancy of organisms, even if the daily temperature reaches 60 F.

There is some preponderance of evidence that the fungi live as saprophytes in the epidermis all winter, down-growth preventing their removal by normal desquamation, though reinfection from footwear also occurs.

We encounter the same difficulty in treatment that is common in other infective conditions, such as tuberculosis, syphilis and gonorrhea; and, as in the case of inaccessible cancer cells, destruction in vitro and in vivo is hence vastly different. It is essential that desquamation and exfoliation be constantly induced. Salicylic acid is the best agent for this purpose. Aside from the use of an ointment of ammoniated mercury in secondary pus cases, where it is specific, greasy applications, particularly in the daytime, are not only uncomfortable but ruinous to shoes. Dyes, from tincture of iodin through the list, are disagreeable and of doubtful efficacy.

All vesicles must be broken up, all bullae or lakes buttonholed, loose epidermis removed, soap and water freely used and salicylic acid, from 12 to 100 per cent., employed, as a peeling agent. Powders in socks, shoes and slippers have constituted regular treatment, whether salicylic-sulphur or talcum powder, this at present seeming the more effective, salicylic and sulphur equal parts, or, occasionally the salicylic alone. Salicylic acid beneath air tight adhesive is used for the removal of callosities.

If greasy applications are needed at night, Whitfield's ointment, or a salicylic-sulphur ointment or simple petrolatum is used. Ointment of ammoniated mercury seems ineffective against these fungi. Cases extending over years are reported.

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COMPARATIVE STUDY OF THE KAHN AND WASSERMANN REACTIONS FOR SYPHILIS *

SOBEI IDE, M.D., AND GEORGE J. SMITH

ANN ARBOR, MICH.

Recently Kahn [1] proposed a precipitation reaction for syphilis for which he claims a high degree of sensitiveness and specificity, combined with simplicity and ease in manipulation. These claims led us to investigate this reaction, and this paper will present a preliminary report of our findings. The Wassermann test was carried out with a sheep-cell system and guinea-pig complement. Two antigens were used on each case. One an absolute alcohol extract of human heart muscle, reinforced with 0.4 per cent. cholesterin, and the other acetone insoluble lipoids with cholesterin, proposed by Kolmer.[2] The fixation period was from sixteen to eighteen hours in the icebox.

RESULTS OF REACTIONS

Wassermann Reaction		Kahn Reaction
295	++++	250
25	+++	35
28	++	64
349	Total of more than ++ positive	349
11	+	11
36	±	63
396	+ and ± included	423
1,769	—	1,742
2,165	Grand Total	2,165

The serums were obtained from unselected cases from this hospital, the University Hospital and various state asylums of Michigan. The serums were separated from the clots by centrifugation and were used, as a rule, within twenty-four hours after reaching the laboratory.

Altogether, 2,165 serums were examined with the Kahn and Wassermann reactions. As indicated in the accompanying table, the results of the reactions are identical when more than two plus positives are counted.

* From the Laboratory of the State Psychopathic Hospital, University of Michigan.

1. Kahn, R. L.: Simpler Quantitative Precipitation Reaction for Syphilis, Arch. Dermat. & Syph. **5**:570 (May) 1922; ibid. **5**:734 (June) 1922.

2. Kolmer, J. A.: Am. J. Syphilis **6**:74 (Jan.) 1922.

CONCLUSION

The value of the Kahn precipitation reaction is almost as great as that of the Wassermann reaction on the blood serum. This reaction is now being performed as a check on the Wassermann reaction on all serums sent to this laboratory for examination. The relative ease with which this reaction can be carried out leads us to believe that it will attain wide usefulness in many laboratories. A point particularly in favor of the Kahn reaction is that anticomplementary serums give no difficulty with it. Such serums are either positive or negative, depending in the presence of syphilitic reagin. While this test worked very well on the blood serum, it does not, however, work as well on the spinal fluid as does the Wassermann test. It is believed by the writers on this subject that in the very near future this drawback will be overcome by some worker who will cast light on the matter.

News and Comment

CONGRESS OF FRENCH SPEAKING DERMATOLOGISTS AND SYPHILOLOGISTS

The Congress of French-Speaking Dermatologists and Syphilologists will be held at Strasbourg on the occasion of the celebration of the centennial of Pasteur, July 26 to 28. These are the topics on the program: Desensitization in diseases of the skin, Lavaut (Paris) and Spillmann (Nancy); nevocarcinoma, P. Masson (Strasbourg) and Bruno Bloch (Basel); treatment of primary syphilis, Queyrat (Paris) and Malvoz (Liége); value of various methods of using medicaments in the treatment of syphilis, Milian (Paris) and Bodin (Rennes). Queries with respect to the congress should be addressed to Professor Pautrier, president du bureau d'organisation du congrès, 2 Quai St. Nicolas, Strasbourg.

Abstracts from Current Literature

BACTERIAL ENDOCARDITIS AS A SEQUEL TO SYPHILITIC VALVE DEFECT. Le Roy H. Briggs, Am. J. Med. Sc. **164**:275 (Aug.) 1922.

Although syphilitic endocarditis is quite frequent, bacterial invasion following this condition is rare. Age incidence and changes in the vascularity of the valves are cited as possible factors to account for the infrequency of the two conditions. One case is reported.

Jamieson, Detroit.

THE SIGNS OF FILARIAL DISEASE. B. Blacklock, Am. Trop. M. & Parasitol. **16**:107 (July) 1922.

In 240 cases examined in Sierra Leone no correlation could be established between the "signs of filarial disease" and the occurrence in the blood of *Microfilaria bancrofti.*

Jamieson, Detroit.

THE ELIMINATION OF ARSENIC IN THE URINE OF SYPHILITIC PATIENTS AFTER INTRAVENOUS INJECTION OF ARSPHENAMIN. Charles Weiss and G. W. Raiziss, Arch. Int. Med. **30**:85 (July) 1922.

Three cases of previously treated syphilis were observed following doses of 0.6 gm. arsphenamin. Most of the arsenic passing through the kidneys is eliminated during the first three days, gradually diminishing during the next two weeks, the largest amount being 13.5 per cent. during this period. Following the second and third doses the elimination is greater and varies considerably in different persons and even in the same person at different times under the same conditions. A quantity of arsenic is temporarily retained by the liver, kidneys, spleen, etc., and some is eliminated through the feces.

Jamieson, Detroit.

SOME NOTES ON INDIAN CALLIPHORINAE. PART VI. HOW TO RECOGNIZE THE INDIAN MYIASIS-PRODUCING FLIES AND THEIR LARVAE, TOGETHER WITH SOME NOTES ON HOW TO BREED THEM AND STUDY THEIR HABITS. W. S. Patton, Ind. J. M. Res. **9**:635 (April) 1922.

PART VII. ADDITIONAL CASES OF MYIASIS CAUSED BY THE LARVAE OF CHRYSOMYIA BEZZIANA VILL, TOGETHER WITH SOME NOTES ON THE DIPTERA WHICH CAUSE MYIASIS IN MAN AND ANIMAL. Ibid., p. 654.

The contents of these articles are described by their titles. They are technical and not suited to abstracting.

Protection of sores and destruction of all larvae is recommended as a preventive in all countries in which these flies exist.

NOTES ON SOME INDIAN APHIOCHAETAE. W. S. Patton, Ind. J. M. Res. **9**:685 (April) 1922.

This is a technical article describing the flies of this species which cause cutaneous and intestinal myiasis in man and animals.

A NOTE ON SOME CULTURAL PHASES OF LEISHMANIA DONOVANI. B. M. Das Gupta, Ind. J. M. Res. **9**:809 (April) 1922.

This is a discussion with regard to the encystment of the Leishman-Donovan bodies and whether unrecognized forms can exist in the tissues of its vertebrate host.

GATÉ-PAPACOSTAS REACTION IN LEPROSY. D. A. Turkhud and C. R. Avari, Ind. J. M. Res. **9**:850 (April) 1922.

One hundred and sixteen cases of leprosy tested by the formol-gel test all gave a positive reaction. This is regarded by the writers as a valuable serologic test in the diagnosis of leprosy.

Jamieson, Detroit.

STUDIES IN ASYMPTOMATIC NEUROSYPHILIS. II. THE CLASSIFICATION, TREATMENT AND PROGNOSIS OF EARLY ASYMPTOMATIC NEUROSYPHILIS. J. E. Moore, Johns Hopkins Bull. **33**:231 (July) 1922.

The author classifies neurosyphilis appearing within a year or less from the date of infection thus: (1) acute syphilitic meningitis; (2) precocious vascular neurosyphilis; (3) neurorecurrence; (4) neurosyphilis manifested by mild symptoms or slight physical signs, not of themselves diagnostic of central nervous system damage (headache, neurologic pains, etc.), and (5) asymptomatic neurosyphilis.

Moore disregards the first three groups, for reasons mentioned in his article, and confines himself to Groups 4 and 5, under the name of early asymptomatic neurosyphilis. The paper is based on 352 cases of primary or secondary syphilis of less than one year's duration. Ninety-four of the 352 patients developed early neurosyphilis, and of this number 76.6 per cent. fell into the asymptomatic group.

The author places the asymptomatic cases in three groups, the grouping being based on the type of spinal fluid, and, in part, on the response of the various types to treatment. He believes that the central nervous system is invaded in most cases in the first year unless the disease is influenced by treatment. Whether the organisms produce clinical neurosyphilis depends on the defense mechanism of the host. It is interesting to note that early asymptomatic neurosyphilis is more common in the white race than in the black, but it is the same in men and women of both races.

Prolonged regular antisyphilitic treatment intravenously will have a favorable result in Groups 1 and 2, but Group 3 responds only to intraspinous medication. The author's statistics do not support the theory of a neurotropic strain.

That the spinal fluid abnormalities of early asymptomatic neurosyphilis are signs of actual anatomic damage to the nervous system is no doubt true. The author believes that Group 1 may pass on to Groups 2 and 3 if left untreated; and he therefore strongly urges a diagnostic lumbar puncture at the end of the first or second courses; if negative, to be repeated at the close of the treatment.

McCafferty, New York.

A REVIEW OF THE CLINICAL SIGNIFICANCE OF THE WASSERMANN REACTION. A. Strickler, J. A. M. A. **78**:962 (April 1) 1922.

This article gives a general summary of the present knowledge concerning the clinical value of the Wassermann reaction. The author stresses the injustice done patients by subjecting them to specific treatment on the strength of a weakly positive reaction, unsupported by clinical evidence of the disease.

REPORT OF A CASE OF NASAL HERPES DUE TO INGESTION OF PHENOLPHTHALEIN. J. Rosenbloom, J. A. M. A. **78**:967 (April 1) 1922.

Recurrent herpes of the nasal region was due to the occasional use of a proprietary pill containing phenolphthalein. Even one-half grain of the drug provoked the eruption.

SOME NOTES ON THE EFFECTIVENESS OF THE VENEREAL DISEASE PROGRAM. H. F. Irvine, J. A. M. A. **79**:1121 (Sept. 30) 1922.

The reporting of veneral disease by number, and not by name, appears to secure better cooperation from physicians. The spending of large sums of money for quarantine and rehabilitation of prostitutes is condemned. Prostitution is handled best by legal means.

SYPHILIS OF THE MOUTH: COMMON TENDENCY OF THE MOUTH AND SKIN TO THE SAME PATHOLOGIC PROCESSES. W. A. Pusey, J. A. M. A. **79**:1285 (Oct. 14) 1922.

This is an exposition of the clinical characteristics of syphilis of the mouth with pertinent comments from the author's experience. Despite the general impression to the contrary, Pusey emphasizes his opinion that leuoplakia due to syphilis is much less frequent than leukoplakia of nonspecific origin.

Michael, Houston, Texas.

BISMUTH IN SYPHILIS. C. Levaditi, Press méd. **30**:632 (July) 1922.

Levaditi discusses in detail the action of tartrobismuth of sodium and potassium in syphilis, from its discovery in 1889 by Balzer to the present time. From a therapeutic point of view, it compares favorably with the best preparations of arsphenamin. Its action is as quick and thorough as that of arsphenamin in all forms of syphilis, whether they be cutaneous, visceral or nervous. The action on the Wassermann test is similar to that of arsphenamin except that the blood which may be positive at the end of a regular course may become negative a short time after the cessation of administration of tartrobismuth sodium and potassium.

It is given in 2 c.c. doses, containing 0.2 gm. of the active substance and injected every three or four days until from 2.2 to 3 gm. are given. An interval of one month is allowed to elapse, and treatment is again given until the Wassermann test becomes negative.

The bismuth is found in all the organs, including the nervous tissue, and is eliminated in the usual ways. Its elimination is begun in twenty hours after an injection, and continues for twenty-five days after the last treatment. There are no contraindications when it is given properly. The compound may be given as a prophylactic, with good results. The author considers it the equiva-

lent of arsphenamin and believes that the patient does not become immune to its action. The good effects of the bismuth continue long after the cessation of treatment.

McCafferty, New York.

PENICILLUM GLAUCUM AS THE ETIOLOGIC AGENT OF ULCER OF THE LEG. U. Rebaudi and G. B. Podesta, Gior. ital. d. mal. ven. **63**: 871 (Aug.) 1922.

Penicillum glaucum was isolated and cultivated from two ulcers of the leg in a middle-aged woman. The complement-fixation test made with the spores of the fungus was strongly positive. The authors call attention to the pathogenic properties of fungi and make a plea to the medical profession for their consideration as etiologic agents of disease.

TREATMENT OF TINEA BARBAE WITH INTRAVENOUS INJECTIONS OF GRAM'S SOLUTION. F. Ronchese, Gior. ital. d. mal. ven. **63**:918 (Aug.) 1922.

Five cases of tinea barbae were treated with Gram's solution. The amount injected varied from 1 to 5 c.c. diluted in 5 c.c. of water, the injections being made every other day. One case showed some improvement, but the other four did not present any change and were finally successfully treated with the roentgen ray. The injections are well tolerated, but there was a local reaction, the vein becoming hard and thrombotic.

Pardo-Castello, Havana, Cuba.

THERAPEUTIC RESEARCHES WITH PERCUTANEOUS ELECTROLYSIS. K. Wirz, Dermat. Wchnschr. **74**:321 (April 8) 1922.

After experimentation, the author found that epinephrin, iontophoretically introduced into the skin, caused a diffuse, intensive and lasting anemia which is useful in small cosmetic operations. Epinephrin, so administered, also favorably influences localized eczema. Ichthyol applied to parasitic sycosis in this manner causes more rapid and certain improvement than any other methods of treatment, including treatment with the roentgen rays. In tricophytosis, iodid of potassium so given causes rapid improvement. In lupus and scrofula these were of little value.

ACID-FAST BACILLI IN ACNE CONGLOBATA. E. Pick, Dermat. Wchnschr. **74**:345 (April 15) 1922.

A case of this disease is reported in which acid-fast bacilli, morphologically characteristic of tubercle bacilli, were observed on animal inoculation and cultural tests. These were conclusively proved to be nonpathogenic saprophytes, and not *B. tuberculosis*.

A NEW TECHNIC FOR INTRAMUSCULAR MERCURY INJECTION. B. Pontoppidon, Dermat. Wchnschr. **74**:348 (April 15) 1922.

Instead of an oil suspension, greater accuracy and sterility is obtained by the use of pellets of cocoa butter containing mild mercurous chlorid (calomel), rod-shaped, with a diameter of a few millimeters, so that they fit into an ordinary 1 c.c. syringe, which is warmed prior to injection.

COLLOIDAL BENZOIN REACTION ON THE SPINAL FLUID. F. MRAS, Dermat. Wchnschr. **74**:369 (April 22) 1922.

After extensive researches on the spinal fluids of syphilitic and non-syphilitic persons, the author advocates the value of the colloidal benzoin reaction and says that there is a second precipitation zone, similar to that described by Kafka in the Mastix reaction, which is of value in the diagnosis of menigitic involvement.

A CASE OF RAZOR CHANCRE. H. HELLE, Dermat. Wchnschr. **74**:376 (April 22) 1922.

The appearance of a chancre on the site of a cut on the chin received in shaving is described. When observed the patient also had a secondary exanthem and a four plus Wassermann.

SYPHILIS OF THE VEGETATIVE NERVOUS SYSTEM. E. SKLARZ, Dermat. Wchnschr. **74**:393 (April 29) 1922.

In the past, little attention has been given this subject. The following subjects are discussed:

The temporary arrhythmias of the heart in syphilitic persons, the appearance of exanthems due to the disease or to the treatment, the Herxheimer reaction, the anaphylactic manifestations subsequent to arsphenamin injections and their relief by sympatheticotropic remedies, syphilis of the suprarenals, alopecia and leukoderma, decubitus and malperforans in neurosyphilitic persons, herpes zoster, the vomiting and hypo-acidity, and the obstipation and incontinence in tabetic patients, their impotence and crises, the occasional appearance of Graefe's and Stelwagon's phenomena without struma, and disturbances of the glands of internal secretion, an instance of which are the anomalies of dental development in persons with congenital syphilis.

THE VALUE OF THE DACTYLOSCOPE IN CRIMINOLOGY. F. DEHNOW, Dermat. Wchnschr. **74**:398 (April 29) 1922.

The dactyloscope is an instrument devised for the observation of the papillary line. In no two fingers is this line the same. Observations of it, to supplement finger prints, have proved of value in the identification of various persons.

ANDREWS, New York.

Book Reviews

ATLAS DER SYPHILIS. By Leo v. Zumbusch. Leipzig, F. C. W. Vogel, 1922.

A recent importation, von Zumbusch's Atlas should have great vogue in this and other countries. The Atlas consists of thirty-one plates portraying sixty-three phases and features of syphilis, as ordinarily encountered, rather than the bizarre and rare manifestations. The choice of subjects is unusually good. The text is short, and is printed with each picture. Indeed, one without any knowledge of German may review the Atlas with profit. One cannot say too much regarding the faithfulness of reproduction of the lesions of syphilis.

LEHRBUCH DER HAARKRANKHEITEN. By Max Joseph. Leipzig: Barth, 1921.

The second edition of this manual of the care and treatment of diseases of the hair has been condensed a little, yet all that is new and has been confirmed has been added. There are twenty-five illustrations in the text, and more than 100 prescriptions. An addenda carries a list of ninety-eight prescriptions for alopecia, hair dyes, hair oils, hair tonics, washes, pomades and soaps.

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Alopecia and Its Treatment. L. K. McCafferty, New York M. J. & Med. Rec. **116**:369 (Oct. 4) 1922.

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